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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

JOINT MEETING

OF THE

NONPRESCRIPTION DRUGS AND ANTIVIRAL DRUGS

ADVISORY COMMITTEES

Pages 1 thru 295

Bethesda, Maryland
December 1, 1998

MILLER REPORTING COMPANY, INC.
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NONPRESCRIPTION DRUGS AND ANTIVIRAL DRUGS

ADVISORY COMMITTEES

Tuesday, December 1, 1998

8:30 a.m.

Versailles Rooms I and II

Holiday Inn

Bethesda, Maryland

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

2 **Call to Order and Introductions**

3 **Eric P. Brass, M.D., Ph.D.**

4 DR. BRASS: I'd like to call this Joint Meeting of
5 the Nonprescription Drugs Advisory Committee and Antiviral
6 Drugs Advisory Committee to order, please.
7 This morning, the two Committees are meeting to
8 discuss the prescription-to-OTC switch of Denavir for the
9 indication of recurrent herpes labialis.
10 I'd like to begin, because this is a very large
11 group, by going around the room and introducing the
12 relatively large panel.
13 DR. NEILL: I am Richard Neill. I am an Assistant
14 Professor of Family Practice and Community Medicine at the
15 University of Pennsylvania.
16 DR. KRENZELOK: I am Ed Krenzelok. I am Director
17 of the Pittsburgh Poison Center and a Professor of Pharmacy
18 and Pediatrics at the University of Pittsburgh.
19 DR. BLEWITT: I am George Blewitt, Industry
20 Liaison Representative to the Nonprescription Drugs Advisory
21 Committee.
22 MS. HAMILTON: Kathleen Hamilton, Senior Advisory
23 to Governor-Elect Gray Davis of California, Consumer
24 Representative on the NDAC Committee.
25 DR. KODA-KIMBLE: I am Mary Ann Koda-Kimble, Dean

1 of the School of Pharmacy at University of California at San
2 Francisco, on the NDAC Committee.
3 DR. McGRATH: Patricia McGrath, University of
4 Western Ontario, Professor of Pediatrics.
5 DR. LIPSKY: Jim Lipsky, Director of Clinical
6 Pharmacology, Mayo Clinic, Rochester, Minnesota.
7 DR. MASUR: Henry Masur, from the Critical Care
8 Medicine Department, Clinical Center, NIH.
9 DR. BRASS: Eric Brass, Chair of the Department of
10 medicine at Harbor-UCLA Medical Center, and Chair of the
11 Nonprescription Drugs Advisory Committee.
12 DR. TITUS: I am Sandy Titus, and I am the
13 Executive Secretary for the NDAC Committee.
14 DR. EL-SADR: I am Wafaa El-Sadr, from the
15 Division of Infectious Diseases at Harlem Hospital, New
16 York.
17 DR. DIAZ: I am Pamela Diaz, from the Chicago
18 Department of Health, Medical Director of Communicable
19 Diseases.
20 DR. YOGEV: Ram Yogev, Children's Memorial
21 Hospital, Chicago.
22 DR. WOOLSON: I am Robert Woolson. I am a
23 biostatistician at University of Iowa.
24 DR. LAUGHLIN: Kathy Laughlin, Chief of the
25 Virology Branch, Division of Microbiology and Infectious

1 Diseases, National Institute of Allergy and Infectious
2 Diseases.
3 DR. REEVES: Bill Reeves, Centers for Disease
4 Control and Prevention.
5 DR. OLIVO: Paul Olivo, Department of
6 Microbiology, Washington University.
7 DR. LECHTER: Karen Lechter, Food and Drug
8 Administration.
9 DR. WU: Teresa Wu, Medical Officer, FDA.
10 DR. JOLSON: Heidi Jolson, Director of the
11 Division of Antiviral Drug Products at FDA.
12 DR. KATZ: Linda Katz, Deputy Director of the
13 Division of Over-the-Counter Drug Products.
14 DR. MURPHY: Dianne Murphy, FDA.
15 DR. BRASS: I think that end microphone might not
16 be working properly.
17 I'd now like to ask Dr. Titus to read the Conflict
18 of Interest Statement.
19 **Conflict of Interest Statement**
20 DR. TITUS: The following announcement addresses
21 conflict of interest issues associated with this meeting and
22 is made a part of the record to preclude even the appearance
23 of a conflict.
24 Based on the submitted agenda for the meeting and
25 all financial interests reported by the participants, it has

1 been determined that all interests in firms regulated by the
2 Center for Drug Evaluation and Research which have been
3 reported by the participants present no potential for
4 conflict of interest at this meeting, with the following
5 exceptions.
6 In accordance with 18 USC Section 208(b), full
7 waivers have been granted to three individuals: Dr. Masur,
8 Dr. El-Sadr, and Dr. Feinberg. A copy of these Waiver
9 Statements may be obtained by submitting a written request
10 to the agency's Freedom of Information Office located at
11 Room 12A-30 of the Parklawn Building.
12 In the event that the discussions involve any
13 other products or firms not already on the agenda for which
14 an FDA participant has a financial interest, the
15 participants are aware of the need to exclude themselves
16 from such involvement, and their exclusion will be noted for
17 the record.
18 With respect to all other participants, we ask in
19 the interest of fairness that they address any current or
20 previous financial involvement with any firm whose products
21 they may wish to comment upon.
22 DR. BRASS: Thank you.
23 I'd now like to ask Dr. Heidi Jolson to present
24 the FDA introduction.
25 **FDA Introduction**

1 **Heidi M. Jolson, M.D.**

2 DR. JOLSON: Thank you, Dr. Brass, and good
3 morning, ladies and gentlemen. It is always tough to be the
4 first one to try the microphone for the day.
5 I'd like to start by welcoming our returning
6 members from both advisory committees and extend a welcome
7 to consultants and guests who are joining us today. We are
8 also pleased to have participation from our sister agencies,
9 the NIH and the CDC, for today's meeting.
10 Today's meeting is convened to discuss an
11 application submitted by SmithKline Beecham requesting a
12 switch from prescription to over-the-counter status for
13 their topical antiviral penciclovir creme.
14 As an introduction, I'd like to take a few moments
15 to discuss the objective for today's meeting and to provide
16 a brief overview of the type of data that will form the
17 basis for today's discussions. This afternoon, Dr. Linda
18 Katz from the Division of Over-the-Counter Drug Products
19 will provide an overview of the OTC switch process in the
20 context of a charge to the joint committees.
21 Penciclovir creme was approved as a prescription
22 product for the treatment of herpes labialis in 1996. This
23 approval was supported by evidence from adequate and well-
24 controlled studies that demonstrated a modest clinical
25 benefit and an acceptable safety profile when used as

1 directed in immunocompetent patients.

2 Based on the data provided, the agency determined

3 that the risk-to-benefit ratio for this product was

4 favorable for prescription drug approval.

5 The purpose of today's meeting is not to

6 deliberate on the original assessment of approvability but

7 to consider the risk-to-benefit ratio in a new scenario and

8 that of over-the-counter use.

9 Consideration of OTC use of an antiviral product

10 is similar in some respects with evaluation of non-

11 antimicrobial OTC switch candidates. Each requires a need

12 to assess issues related to disease self-recognition, the

13 potential for product misuse, the ability of consumers to

14 comprehend the label instructions, and the need to consider

15 safety for the individual patient.

16 However, consideration of a product for OTC

17 treatment of a transmissible disease raises an additional

18 complicating factor, and that is the potential impact on

19 resistance, an issue of broad public health importance.

20 There are currently no antiviral products that are

21 available over-the-counter in the United States. Only one

22 application for an Rx-to-OTC switch has been considered by

23 the Antiviral Drugs Advisory Committee, and this application

24 was not recommended for approval. This previous application

25 requested consideration of a switch for oral acyclovir for

1 the treatment and suppression of recurrent genital herpes.
2 As will be discussed today, both applications raise some
3 common issues about the potential for misuse and the
4 potential impact on viral resistance patterns. These
5 applications also differ in several important respects,
6 including likely implications due to differences in route of
7 administration and differences in the intended indications.
8 I'd like to turn next to comment briefly on the
9 nature of the data that will be reviewed today in support of
10 this application. The database in support of an Rx-to-OTC
11 switch is different from the data that is typically reviewed
12 by the Antiviral Committee in support of prescription
13 approval.
14 In addition to the studies that form the basis of
15 this product's original approval, the applicant has provided
16 results from post-marketing safety experience, results from
17 studies designed to assess consumer comprehension of
18 proposed draft labeling, an actual use study intended to
19 provide information on likely use in a similar-to-OTC
20 setting, and available information on the presence of herpes
21 virus resistant to penciclovir or acyclovir. Each of these
22 pieces will be very important to consider in today's
23 discussion.
24 And last, we recognize that the committees' charge
25 to make a recommendation about OTC availability for this

1 product is not a simple task. We additionally recognize
2 that several important issues, including the implications
3 for viral resistance and the potential for misuse, cannot be
4 fully evaluated in advance of an actual OTC switch.
5 We will therefore ask for your scientific judgment
6 on these issues and ask you to weigh the risks and benefits
7 of over-the-counter availability both from the perspective
8 of the individual patient and from the broader public health
9 perspective.
10 Thank you in advance for your guidance today, and
11 we will look forward to the committees' consideration of
12 this Rx-to-OTC switch application.
13 DR. BRASS: Thank you.
14 The next portion of the presentation will be the
15 sponsors--in this case, SmithKline Beecham. They have been
16 scheduled for an hour. I would ask the committee members
17 and consultants to hold any detailed explanatory questions
18 until the end of the complete sponsor presentation and ask
19 only questions that are points of clarification, et cetera.
20 With that, I'd like to introduce Dr. Lynn Marks,
21 Vice President and Director, Medical Regulatory and
22 Toxicology, SmithKline Beecham.
23 **SmithKline Beecham Presentation**
24 **Introduction and Medical Regulatory Overview**
25 **Lynn Marks, M.D.**

1 DR. MARKS: Thank you, Dr. Brass.

2 Good morning, ladies and gentlemen. I am Lynn
3 Marks, Vice President and Director of the Medical Regulatory
4 and Toxicology Groups for SmithKline Beecham Consumer Health
5 Care.

6 We are delighted to have the opportunity to
7 discuss with you our proposal to switch denavir from Rx to
8 OTC status for the treatment of recurrent herpes labialis,
9 most commonly known as cold sores.

10 [Slide.]

11 DR. MARKS: Our rationale for the denavir switch
12 centers on these four points. Denavir fulfills the OTC
13 criteria; the OTC environment will indeed enhance
14 accessibility; and this enhanced accessibility will improve
15 treatment management; and in the OTC environment, we are
16 convinced that denavir is unlikely to increase the incidence
17 of resistance.

18 [Slide.]

19 DR. MARKS: I am pleased to have joining me today
20 Dr. Spotswood Spruance and Dr. Myron Levin, and I will read
21 the Conflict of Interest information. Both Dr. Spruance and
22 Dr. Levin have received reimbursement from SmithKline
23 Beecham for their roles as investigator in clinical studies,
24 for consultation services, and for speaking engagements.
25 Neither has a financial interest based on the outcome of

1 this meeting or FDA approval of the OTC switch. The
2 services provided to SmithKline Beecham are of a similar
3 nature to those they provide to other pharmaceutical
4 companies.
5 Dr. Spruance, who is arguably the world's expert
6 on the clinical management of cold sores, with over two
7 decades of interest in research in clinical management of
8 this disease, is going to talk to us about the disease, he
9 is going to talk to us about how important denavir is in
10 terms of the management of that aspect.
11 Dr. Myron Levin, who is a renowned teacher,
12 researcher and clinician, who is on the original paper that
13 was published in the New England Journal of Medicine dealing
14 with the first case of acyclovir-resistant herpes simplex,
15 will be speaking to us about the issue of antiviral
16 resistance.
17 [Slide.]
18 DR. MARKS: Our agenda today--I'll give you a
19 brief medical and regulatory overview, followed by Dr.
20 Spruance talking about denavir, mostly from the NDA studies
21 in terms of the safety and efficacy; and then Dr. Levin will
22 talk about the resistance issues, and I will come back and
23 close with our case for OTC status.
24 [Slide.]
25 DR. MARKS: Let's start at the beginning.

1 Famciclovir and penciclovir. Famvir is the oral pro-drug
2 formulation of penciclovir; it is converted in the body into
3 its active moiety, that of penciclovir. The point is that
4 we feel this is relevant in terms of the active chemical, in
5 terms of the safety profile when we look at the package of
6 information that is available on the substance that we are
7 discussing today.
8 Denavir--a different brand name--topical
9 formulation as opposed to an oral or systemic formulation.
10 It goes directly into the skin and works locally, again with
11 the active chemical entity being penciclovir.
12 [Slide.]
13 DR. MARKS: The regulatory status around the
14 world, as was mentioned earlier, denavir was initially
15 approved in the U.S. in 1996. We currently have approvals
16 in 46 countries around the world, and in 13 of those
17 countries, we have approvals for marketing without a
18 prescription.
19 [Slide.]
20 DR. MARKS: How common are cold sores? Very
21 common. Over 40 million adults in the U.S. alone, with 65
22 percent of those having two or more recurrences per year.
23 The disease lasts on average one week, and it is associated
24 with pain, self-consciousness and loss of self-esteem. And
25 probably the most unfortunate part about this disease is the

1 fact that it is recurrent in nature; it is unpredictable and
2 unwelcome, like when you are getting ready to have a family
3 photograph, or perhaps when you are getting ready for an
4 advisory committee meeting.
5 [Slide.]
6 What kind of treatment options are available?
7 Home remedies, ranging from alcohol to ice cubes; OTC
8 monographs--there are two tentative final monographs dealing
9 with topical anesthetics and skin protectants; and then, the
10 first and only prescription medication approved for the
11 treatment of recurrent cold sores in healthy adults, that
12 being denavir.
13 [Slide.]
14 The current situation--in terms of the management
15 of cold sores, almost three-fourths of individuals seek
16 effective treatment. Over half believe there is really
17 nothing you can do about the disease, that it just needs to
18 run its course, and that there is a low awareness of the
19 viral etiology associated with this disease, and that
20 because of the products that are currently available,
21 treatment can be initiated at any time--a 50-50 split in
22 terms of whether it is important to start early or late,
23 because most of the other products deal with anesthetics and
24 skin protectants as opposed to the viral etiology.
25 [Slide.]

1 So, how do people seek care when it comes to the
2 medical community?
3 Three-fourths of the individuals don't see a
4 doctor. Either they don't have a doctor, they don't want to
5 go to the expense of seeing a doctor; the cold sore comes
6 and goes before they have time to make an appointment and
7 get to the doctor. There are various reasons.
8 The other fourth of the individuals do consult a
9 physician, but more than 60 percent of those individuals are
10 there for another reason and just mention the fact that they
11 are also troubled by cold sores. If they do talk to their
12 physician about cold sores, a little less than half actually
13 receive a prescription medication, a prescription of some
14 kind for the management of their disease.
15 But importantly, even if the individual receives a
16 prescription, more than 90 percent of those people wait
17 until they have a cold sore outbreak before they go and get
18 the prescription filled.
19 [Slide.]
20 We believe that the prescription status of denavir
21 limits the access to the therapeutic benefits. What do I
22 mean by that?
23 Let's say, for instance, I am a cold sore
24 sufferer, and last night in my room, as I am looking over my
25 slides getting ready for a talk, the anxiety associated with

1 presenting to you today, I notice the first sign or symptom,
2 a tingle coming on--the impending cold sore outbreak. If I
3 have thought about it in advance, maybe I have gotten my
4 prescription filled, and I have a tube of medication with me
5 on the road. Since I traveled from another State, my
6 physician may not be readily available, and if I don't have
7 my medicine with me, rather than going down to the hotel
8 gift shop, the local pharmacy, to pick up the medication
9 that has been proven to speed the healing of my cold sore, I
10 have to wait. I can't begin to manage my disease, even
11 though I can recognize the signs and symptoms and even
12 though I could have ready access if I had the tube with me.
13 Next, I'd like to ask Dr. Spruance to come up and
14 give you a little more information about the disease and the
15 clinical studies and safety data from our NDA application.
16 We are going to show you information that was not in the
17 original NDA as well as the efficacy data from the NDA. The
18 purpose of that is not to discuss whether one is better than
19 the other, but rather, to help you understand why it is that
20 when we are approached by outside people asking, Why is your
21 regulatory information in another country different, why is
22 the Journal of the American Medical Association article on
23 the efficacy of this product different, we can show you very
24 briefly how to put that into perspective showing the two
25 different ways of looking at similar kinds of data and

1 coming to the same conclusion--that is, that denavir speeds
2 the healing of cold sores.
3 Dr. Spruance?
4 **Efficacy and Safety of Denavir**
5 **Spotswood Spruance, M.D.**
6 DR. SPRUANCE: Thanks, Lynn.
7 It is a pleasure to be here and talk about cold
8 sores and have this subject of cold sores be in a large
9 public forum like this. I think that cold sores are a
10 neglected form of herpes. The emphasis has been on genital
11 herpes and its management, but I think that people with
12 herpes labialis suffer to a similar degree in the
13 complications associated with oral facial herpes that are of
14 major medical significance as well.
15 [Slide.]
16 As Dr. Marks mentioned, I have been involved with
17 the investigation of the treatment and the pathogenesis of
18 herpes labialis for 25 years as a professor at the
19 University of Utah School of Medicine. During that time, I
20 have been particularly interested in the biologic and
21 pharmacologic factors that influence the effect of
22 treatment.
23 As you are probably aware, treatments have become
24 available for genital herpes and have been slow in coming
25 for herpes labialis, so it has been a very interesting

1 problem to try to develop an effective therapy for this
2 condition.
3 [Slide.]
4 So what I am going to do today is, first of all,
5 present the efficacy and safety data from the denavir
6 clinical trials. I think this data will show you that there
7 is a meaningful clinical benefit to the patient from denavir
8 treatment. And last, I am going to go over the natural
9 history of herpes labialis, and I am going to talk
10 particularly about the rapid onset of the disease and how
11 this influences the way in which treatment has to be
12 administered.
13 [Slide.]
14 What about the impact of herpes labialis? This
15 disease is important because it is enormously common. One
16 in every five people in the world and in the United States
17 have an episode of herpes labialis sometime in their lives,
18 and the majority of people who have the disease get it two
19 to four times a year. The average duration is about a week,
20 but some people have it as long as two weeks.
21 The frequency of the disease is about two to four
22 episodes a year for most people who have the illness, and as
23 I mentioned, this isn't trivial to people who have it.
24 People don't talk about it. It is not in the media that
25 these people are uncomfortable or suffering. But my son has

1 it--Lynn was telling some stories, and I guess I can talk
2 about my family, my mother, my son. And I talk to patients
3 in the clinic, and these people are really bothered. They
4 are disfigured, they have pain, and they are emotionally
5 down. They don't feel right. They've got this lesion right
6 on their lips where everybody can see it, and they want it
7 to go away, and they feel that the health professions have
8 not adequately addressed this particular concern and haven't
9 brought them treatments or thought about them as much as
10 they have for herpes genitalis, for example.
11 [Slide.]
12 So let's go over the natural history of the
13 condition and see what this tell us about how we can best
14 intervene with the treatment.
15 The disease is caused by herpes simplex virus Type
16 1, or HSV-1, and as you know, HSV-2 causes genital herpes,
17 and to some extent, HSV-1 is also involved in genital
18 herpes.
19 So this is a childhood infection to a large
20 extent. That is, in the first five years of life, children
21 acquire it like they did measles, mumps and rubella, before
22 we had vaccines. And it is passed in families and in
23 nursery schools by contact with infected saliva.
24 In addition, there is a slow and further
25 acquisition of the virus, one to two percent a year among

1 older children, adolescents and young adults up to age 25.

2 In addition to causing in some patients an

3 inflammatory condition of the oral cavity, the virus enters

4 sensory nerve axons and is transported to the neural

5 ganglia, in this case, the ganglia of the trigeminal nerve,

6 the fifth cranial nerve, where it establishes a chronic

7 latent infection for life, and remains dormant until it is

8 reactivated.

9 This process of a primary infection and the virus

10 going up and establishing latency in the ganglia, the best

11 evidence we have is that this is not repeated, so that once

12 you are infected with your first virus that you have

13 acquired, say, in nursery school or from a family member,

14 this doesn't happen again. You have the virus that you came

15 with, that you started with, and you don't get infected

16 multiple times and have multiple different kinds of viruses

17 in your neural ganglia.

18 This is important, as Dr. Levin will point out,

19 when we talk about ways in which the development of

20 resistance could potentially be a problem, and he will

21 demonstrate to you how the natural history will make that

22 difficult to occur.

23 [Slide.]

24 This slide illustrates some of these factors.

25 Here is the latent herpes simplex virus in the ganglion of

1 the trigeminal nerve, and following an appropriate
2 reactivation signal, such as the common cold, if you will,
3 cold sores, fever, stress, an advisory committee meeting,
4 ultraviolet light, going out in the sun, the virus
5 reactivates. Exactly how that takes place is a very
6 interesting question, and many people are working on it, but
7 let's just say the mechanism is somewhat moot at this time.
8 The virus then migrates or is transported back
9 down the sensory axons to the skin, where it initiates a
10 recurrent infection of the skin in a patient, of course, who
11 is already immunocompetent, who has plenty of immune
12 responses to the virus, so that only a brief period of
13 replication occurs. Again, this is important to remember as
14 we consider how treatment needs to be delivered.
15 [Slide.]
16 I am going to go over the stages of herpes
17 labialis and talk about the way in which the disease evolves
18 in consideration of what I have just told you about the
19 infectious agent and the pathogenesis.
20 This diagram is on the vertical axis and shows the
21 relative clinical severity of the different stages of the
22 disease, and down on the horizontal axis, we have the time
23 in days.
24 The infection begins with either prodromal
25 symptoms, or you get some redness, or some people have just

1 a papule or a bump as their first sign or symptom. But most
2 people will have a prodrome, that is, some itching, tingling
3 or burning at the site of the incipient attack, and this is
4 a good time to start medication. If you can have it
5 available and have it in your hand when you know the
6 infection is first beginning, you can most appropriately and
7 most effectively decrease the duration of the episode.
8 Yo can see that these first stages are very mild
9 in the degree of clinical severity, and when someone just
10 has the first stages, and it doesn't go any further--we call
11 these aborted episodes of herpes labialis--for reasons
12 associated perhaps with the amount of virus that gets to the
13 skin or the type of aggressiveness of the immune response on
14 a particular day, the virus effort to invade the skin is
15 thwarted, if you will, and that is all you get.
16 [Slide.]
17 This occurs 25 percent of the time; the other 75
18 percent of the time, the disease goes on to what we call
19 classic herpes labialis, and this is the real problem that
20 people are worried about. The skin is broken down, there is
21 focal destruction of the epithelium; it starts off with a
22 blister and goes on, as I will show you, to an ulcer. And
23 this is what people are worrying about. They are saying,
24 Oh, my gosh, there goes the week. I've got this large
25 lesion right on my lip where people are looking at me. This

1 is going to be a bad period of time. I hope I am not doing
2 anything important this week.
3 What I want to show you here about the vesicle
4 stage is this is really the greatest degree of severity that
5 the disease presents. It is one in which there is in most
6 patients continuous pain, and the pain is made worse by
7 eating and talking, because you are moving your lips, where
8 the lesion is located.
9 The other thing that I need you to see is how
10 vertical this line is, how extremely rapidly the disease can
11 progress from these earlier signs and symptoms that herald
12 the beginning of a sore to a fullblown lesion. In literally
13 eight hours, overnight, it can progress that rapidly from
14 the first warning signs to full maturity. And of course,
15 this is going to bear on the need to treat as soon as
16 possible.
17 [Slide.]
18 Here is a patient with a vesicular lesion of
19 herpes labialis.
20 [Slide.]
21 Then it goes on to the ulcer stage. With the
22 proteases and other enzymes released by the inflammatory
23 response in the skin that has been triggered by the
24 reappearance of the virus in an immunocompetent patient, the
25 stratum corneum covering the surface of the vesicle will

1 break down, and then you have the appearance of the ulcer.
2 The ulcer is also at a relatively severe stage, with a
3 significant degree of pain; there is a lot of virus present.
4 If you do swab cultures of a herpes labialis ulcer, you are
5 going to find high titers of virus, so this is a
6 particularly infectious stage as well.
7 [Slide.]
8 Then, the longest stage is the hard crust stage.
9 In this particular example, it is lasting five days. You
10 can see that it is a little bit less severe. Pain is less
11 during this stage, but sometimes during eating or talking,
12 the crust will crack open, with the recurrence of pain.
13 [Slide.]
14 Here is a crusted herpes labialis lesion.
15 [Slide.]
16 Here are all the stages put together--the vesicle,
17 the ulcer and the crust. At this point, when the crust
18 falls off, where you see the line, that is effectively the
19 end of a herpes labialis episode as far as the patient is
20 concerned. We also use this endpoint in clinical trials.
21 You'll here us talk about "time to loss of crust" because it
22 is a convenient and I think quite accurate endpoint; there
23 is nothing equivocal about having the scab fall off for
24 either the patient who is making the observations or
25 multiple investigators in different study sites.

1 There are a few abnormalities that persist in the
2 skin--there can be a little bump or a little flaking of the
3 skin--but they are not of major significance.
4 [Slide.]
5 So, how does this all relate to the timing of
6 treatment? I think you can see that you need to get this
7 product on as soon as possible to have the greatest impact
8 on the therapy. This is a viral disease. The drug acts by
9 inhibiting replication of the virus, and therefore, the
10 degree to which you can get in and block the replication of
11 a virus is going to be a quite precise reflection of how
12 much efficacy you are going to have in clocking the actions
13 of the destructive effects of the virus on cells.
14 So this is a very time-sensitive product, if you
15 will, because of the way in which it acts in interfering or
16 blocking the growth of the pathogen that causes the disease.
17 I feel that the prescription status, therefore, in
18 which there is going to be inevitable delays associated with
19 calling your doctor, getting the prescription, getting it
20 filled, are going to allow the virus to replicate a critical
21 few further additional hours with progression of the
22 pathogenesis of the lesions to a point where, if you then
23 put it on, you will have a more limited type of efficacy
24 available from the product, and therefore, if you have it
25 more readily available in the OTC environment, you can get

1 the maximum clinical benefit from this product.

2 [Slide.]

3 This brings me to what I call the treatment

4 paradox for herpes labialis. There are a number of

5 nonspecific treatments available that you probably already

6 know about. There is Blistex and Camphophenique and

7 Viractin and Herpecin, and products that give symptomatic

8 relief. These products have no need for early treatment.

9 They will have their effect on reducing the discomfort from

10 a cold sore no matter when you put them on in the course of

11 the illness, and they are available OTC as fast as you can

12 want to get them; just walk into the drugstore. And

13 paradoxically, the product that is time-sensitive, denavir,

14 that inhibits the replication of the pathogen and has to be

15 put on right away, well, that is available by prescription

16 and not OTC, so there is a delay associated with getting it.

17 So that is a bit of a paradox in my mind.

18 [Slide.]

19 Let's go on and talk about the denavir clinical

20 trials and a little bit about how they were analyzed and,

21 without dwelling on this, let's try and expand some of the

22 information that you have.

23 These were extraordinarily well-done,

24 comprehensive clinical trials. There were two of them. One

25 was in Europe, called Trial 025, and one was in the United

1 States, called Trial 024, and the total number of patients
2 involved in the trials was 3,000.
3 The admission criteria were extremely broad so
4 that the results are applicable to almost everyone with
5 herpes labialis. The design of the trial and the criteria
6 for starting the drug, administering the drug, were the same
7 as those that are being proposed for the OTC environment--
8 that is, the concentration of drug, the dosing regimen, the
9 patient-initiated format of the trial are all similar to how
10 the drug would be used in OTC so the results of the trial
11 should be applicable to the OTC environment usage.
12 The other thing the trial demonstrated was that
13 patients could self-diagnose for herpes labialis extremely
14 accurately. Only three of the 3,000 patients in the trial
15 put denavir on something other than herpes labialis. This
16 reflects my experience in the clinic. The patients know
17 when they are getting herpes labialis--something that comes
18 over and over again in your life, you get pretty good at
19 knowing what it is, when it is coming, and there are not a
20 lot of other things around the lips and around the borders
21 of the mouth that look like this or feel like this.
22 [Slide.]
23 What about the efficacy of these trials? What
24 they showed was that denavir was highly statistically
25 significantly better than the vehicle in reducing the

1 healing time of lesions, and the degree of benefit was
2 modest, but of reasonable and of clinical significance to
3 the patient.
4 [Slide.]
5 Let's go over the efficacy data a little bit more.
6 I want to talk about two ways in which the data was
7 analyzed, particularly lesion healing data. The first way
8 of analyzing the data was performed by SmithKline Beecham
9 and formed the basis of the NDA and was done in coordination
10 with the FDA and under their direction. This involved
11 studying a combination of both the aborted lesions that I
12 described and the classical lesions in determining the
13 effect of the drug. So we see consideration of the papule
14 stage as well as the more severe stages of the disease.
15 This is the data that you'll see in your briefing
16 document, and it is in the package insert, and the degree of
17 efficacy that is involved reflects what was found in that
18 analysis.
19 Now, the analysis that I did and published in the
20 Journal of the American Medical Association in 1997 was a
21 bit different. This was a prospectively, protocol-defined
22 analysis that involved looking at just the classical
23 lesions--in my opinion, the part of the disease that really
24 matters to the patient. The patient wants to know what
25 happens from this product when I put it on the real disease,

1 not what happens when I put it on a part of the disease that
2 goes away and doesn't mean much to me.
3 We then had these two analyses, and the term
4 "critical" has been invented here, so the neologis [ph.] and
5 critical lesion stages here to reflect the NDA analysis and
6 the protocol-specified analysis involve, again, classical
7 lesion stages.
8 [Slide.]
9 Let's look at what the results were using these
10 two different kinds of analyses. In the NDA analysis, there
11 was a faster time to healing for denavir on the order of
12 half a day, and similarly for loss of pain--it occurred
13 approximately half a day shorter for those who got denavir.
14 [Slide.]
15 Here was the protocol-specified analysis of the
16 drug's effect on classical lesions, and it is broken down
17 here in a couple of ways, first of all, by study--Study 024
18 in the U.s. and Study 025 in Europe. We have investigator-
19 assessed data--that is, every day the patient came in--so we
20 have a daily record of what the investigators thought about
21 the lesions. The patients also assessed their lesions four
22 times a day, so we have slightly more frequent observations
23 from the patients. Both showed efficacy, both were highly
24 statistically significant. And the degree of difference, as
25 you can see down here, was on the order of .7 to one day's

1 difference in favor of denavir. So by this analysis, there
2 was a great effect.
3 Both analyses are based on the data and both can
4 be supported and are accurate; they are just different ways
5 of looking at the information.
6 [Slide.]
7 So what can we say just in general about the
8 efficacy of denavir, because obviously, one of the reasons
9 we are here is to consider the risk-benefit ratio as it
10 applies to the application for OTC status.
11 Well, importantly, this is the first universally
12 convincing conclusive data that herpes labialis is a
13 treatable disease. I have been around for 25 years, and
14 there are data and drugs that have come close, and they
15 probably are effective, but nobody has really shown that
16 this is treatable until these SB trials.
17 This has thus become the only FDA-approved product
18 for recurrent cold sores in healthy subjects, and again, I
19 think this is a major accomplishment, and I am very pleased
20 for the patients who have the disease that industry and the
21 FDA have gotten together and put something out there that is
22 known to be effective.
23 So what conclusive or final statement can we make
24 about exactly what the product does? Well, in my opinion,
25 the NDA analysis showing half a day is really a worst case

1 type of presentation. It is a very strenuous, conservative
2 approach to the data. It is really important to stress the
3 data, see how robust it is, and determine do we have an
4 effective product here, a statistically significantly
5 effective product. You have to do this to data to make sure
6 where you are. So that is important.
7 But as a clinician, I like looking at what the
8 drug does to the classical lesions, and I lean toward the .7
9 to one-day benefit that is shown by the analysis of
10 classical lesions that I presented in my paper in JAMA in
11 1997.
12 Further, if you look at patients who are compliant
13 in the study, that is, took the medicine as prescribed--and
14 you know that in these trials, when you look at intent-to-
15 treat studies, you will have some people, for example, who
16 don't take the drug--if you look at the compliant
17 population, you can get even an additional degree of benefit
18 can be found in the dataset.
19 So I like to think of this drug as being able to
20 effect about a 20 percent improvement in the course of the
21 disease, about a day's benefit for somebody who has a five-
22 day lesion and a two-day benefit if a patient has one of
23 these more aggressive lesions that can last as long as 10
24 days.
25 [Slide.]

1 The safety of denavir has been excellent in
2 clinical trials. There were no serious adverse events, and
3 the adverse events that were reported are the kinds of
4 things that are frequently found in the normal population
5 whether or not you are in a study--headache, nausea,
6 diarrhea, low-frequency/no difference between denavir and
7 vehicle control. There were no drug-drug interactions
8 reported and no photosensitization was noted in the trials.
9 [Slide.]
10 Does it burn? Does it cause people stinging and
11 so forth? Is it an irritant? No. Its local application
12 site reactions were extremely infrequent, in the one to 2
13 percent range. There was no difference between penciclovir
14 and placebo. These types of reactions were very mild, and
15 nobody withdrew from the study because of being irritated by
16 the application of the creme.
17 [Slide.]
18 Formal irritancy and sensitization studies were,
19 of course, conducted by the company as well, in part of
20 their Phase 1 investigations, and just to quickly summarize,
21 it is not an irritant even under extremely provocative
22 conditions such as occlusion, higher drug concentrations,
23 two to three weeks of having the drug on the skin. And
24 again, there is no evidence of dermal sensitization in
25 rechallenge studies.

1 [Slide.]

2 In conclusion, I think the data clearly show that
3 this is a safe and effective product for the treatment of
4 herpes labialis and the first such product to be approved in
5 this country. I think the degree of clinical benefit is
6 meaningful to the patients. And lastly, I think the switch
7 to OTC status will ensure that patients are able to get the
8 maximum clinical benefit from the product, because as I
9 mentioned, this is a time-sensitive product, and if you
10 don't get it on or allow the patient to put it on as soon as
11 possible, you are going to lose some of the therapeutic
12 benefit that patients would otherwise be able to obtain.

13 Lynn, that's all. Thank you.

14 DR. MARKS: Thanks, Dr. Spruance, for going over
15 the information that says cold sores are indeed a common
16 illness, an important illness to those individuals who
17 suffer from cold sores. Denavir has an efficacy and safety
18 profile which is compatible with an OTC environment, and I
19 will review more of that information later on in the
20 presentation.

21 Now, I'd like to ask Dr. Myron Levin to go over
22 the package of information that we believe and that
23 convinces us that the OTC environment for denavir is
24 unlikely to increase the incidence of antiviral resistance.

25 Dr. Levin?

1 **Antiviral Resistance**

2 **Myron J. Levin, M.D.**

3 DR. LEVIN: Thank you, Dr. Marks.

4 Good morning, everybody. I am actually a cold
5 sore sufferer, too, and I can remember at least three times
6 when I was giving a talk on herpes simplex virus that I had
7 a cold sore and felt that I was "figure 1" in my talk.

8 I am going to talk to you today about antiviral
9 resistance. This is a topic that I have been interested in
10 for 18 years, since I took care of R.C., the child that Dr.
11 marks talked about, who had a combined immunodeficiency and
12 disseminated herpes simplex, and we treated him then with an
13 investigational drug, and he got dramatically better. I was
14 also there when he had a recrudescence, and we knew that
15 something was wrong when he didn't get better in the same
16 way. He actually eventually improved in spite of the fact
17 that we knew eventually that he had a resistant virus and
18 then went on to die of a bacterial illness. But it
19 certainly piqued my interest, and I took notice of the
20 problem of antiviral resistance.

21 Let me pick up the thread that Dr. Spruance
22 started by just repeating that we have already available
23 denavir as a drug that is available on a prescription basis
24 in the United States for topical therapy of herpes labialis.
25 We know that it is safe, that it is effective. It is almost

1 certain that if the OTC switch occurs, there will be a great
2 increase in the use of antiviral therapy, and it is natural
3 that we worry that there will be some effect on antiviral
4 resistance.
5 With this concern in mind, I'm going to give you
6 the reasons why I am convinced that this will not be a
7 problem and that denavir will not cause any palpable change
8 in antiviral resistance.
9 [Slide.]
10 I base this on three reasons. First, we already
11 have penciclovir's susceptibility data. From HSV isolates
12 that were obtained from numerous trials that SmithKline
13 Beecham has undertaken with both famvir and with
14 penciclovir.
15 Perhaps most important, we have very long
16 experience, more than 15 years, with acyclovir, and I am
17 going to give you the argument that what we know is true of
18 acyclovir is very like to be true of penciclovir.
19 And finally, there are characteristics of both the
20 virus, the host and the treatment that would militate
21 against resistance being likely to change.
22 [Slide.]
23 First, let's start with the last point, the
24 biology of the virus and its treatment. We see in this
25 diagram that in the top box, there is penciclovir. We could

1 just as well have put any other antiviral agent of the same
2 class, nucleoside analogs, in that box. It turns out that
3 for the penciclovir to be active, it has to be activated to
4 its triphosphate form, shown in the bottom box. That
5 process, the activation process, is the result of a herpes
6 virus specified enzyme called thymidine kinase, shown as
7 "TK" here. TK starts the process, and you end up with the
8 activated drug.
9 The activated drug then has to interact with a
10 second herpes virus enzyme, shown here as a herpes simplex
11 virus DNA polymerase, and when the two interact, the
12 polymerase is inhibited, there is no further viral
13 replication, there is no new viral DNA formed, and the virus
14 infection basically is inhibited. It is not a virus sital
15 [ph.] agent--it doesn't kill virus--it just prevents new
16 virus from being made. We'll come back to that point.
17 I show you this for two reasons--first, to make
18 the point that not only penciclovir but acyclovir or other
19 nucleoside analogs could be in the top box. The mechanism
20 of action is very similar. The second point is that one
21 might assume, and in fact it will turn out, that if the
22 virus develops mutations in either of those enzymes, there
23 will be viral resistance as a potential outcome.
24 For example, if the herpes simplex virus TK, the
25 first step, developed mutation so that it could not activate

1 the drug, you wouldn't have the active drug and therefore no
2 inhibition; or if the herpes DNA polymerase were mutated in
3 such a way that it could no longer interact with the
4 activated drug, then of course, you again would not have
5 inhibition.
6 [Slide.]
7 And in fact if one looks at mutants that have been
8 acquired from the community, you can see from the first two
9 bullets that thymidine kinase itself can be mutated, and the
10 first bullet shows that if there is a decrease in the amount
11 of thymidine kinase that is produced so that activation is
12 very low, this is the so-called TK partial mutant, or if the
13 enzyme is not made at all, then you have a total lack of the
14 enzyme, called TK-negative, and together, they make up the
15 class called TK-deficient.
16 So if you can't activate the drug, you are not
17 going to have activity, and you will have resistance. That
18 is by far the most common type of mutation one sees in
19 resistance to these antiviral drugs.
20 A second possibility that is much less common is
21 the enzyme being altered in such a way that it will not
22 activate penciclovir or acyclovir, but will still work with
23 its normal substrate, thymidine. This is the so-called TK-
24 altered type of mutation, and as I said, it is unusual. And
25 then, very rarely, one sees a change in the viral DNA

1 polymerase so that it no longer interacts with the activated
2 drug, and therefore, there is not inhibition of the virus.
3 [Slide.]
4 Now, one can study this in some detail in tissue
5 culture, and the reason it can be studied in tissue culture
6 is because the DNA polymerase of herpes actually makes
7 mistakes, and when it makes mistakes, there is the potential
8 for a significant mutation, and when those mutations occur,
9 which occurs naturally, then you have natural resistance.
10 So the first observation in tissue culture is that
11 if you take any pool or any collection of virus that is
12 growing naturally, and you look for mutants, you will find
13 them. When you find them, you will find that they are
14 mostly TK-deficient; you will find that if they are TK-
15 negative, that is, total loss of enzyme, or if they are TK-
16 partial--most of the time, when they are TK partial, you
17 have a great decrease in the amount of enzyme--then there is
18 cross-resistance between penciclovir and acyclovir.
19 So again to make the point that there is a
20 concordance between what is true of acyclovir is true of
21 penciclovir, because I want to use that fact in a moment.
22 Finally, if you take viruses that were selected as
23 resistant, either by growing them in the presence of
24 acyclovir or in the presence of penciclovir, and then you
25 sequence the thymidine kinase gene and look at the DNA

1 sequences, you'll find that the mutations occur in very
2 similar areas. So again, there is a concordance between the
3 two.
4 [Slide.]
5 If you further, then, take these naturally-
6 occurring mutants and look at them in tissue culture, you
7 can determine what percentage of the total virus is actually
8 resistant. And if you do such an experiment, and you do it
9 with Type 1 herpes, you will find that a very small but
10 quite significant percentage of virus--something like one in
11 2,000 viral particles--is resistant to penciclovir, but you
12 have the same frequency of resistance to acyclovir.
13 This is very similar to what was shown some years
14 ago, so that historically, this phenomenon has been true
15 over many years. And probably very important is the fact
16 that with herpes simplex Type 2--with which, by the way, we
17 have the most epidemiologic data on resistance--we find that
18 the likelihood of a resistant mutant occurring is 10 times
19 higher than with Type 1 herpes, and with the type of disease
20 we are dealing with today, herpes labialis, we are almost
21 always dealing with Type 1 herpes.
22 [Slide.]
23 If we now turn to clinical isolates and study
24 them, we will find once again that they are mostly TK-
25 deficient, so what has been true in tissue culture turns out

1 to be predictive of what is going to happen in the clinic,
2 and certainly the two mirror one another. Because of that,
3 we find once again that TK-altered and DNA polymerase
4 mutants are very unusual. And now that we are dealing with
5 clinical issues, we find, interestingly, that there is no
6 clinical correlate; that if an individual has an acyclovir
7 or penciclovir-resistant mutant, they are still likely to
8 heal their lesions in a timely fashion. There is no
9 difficulty in a normal host as a rule--there are very few
10 exceptions--dealing with resistant virus.
11 [Slide.]
12 The reason for that can probably be explained by
13 this table. If you look on the far right, where it says
14 "immunocompromised," and you look at the immune system in
15 the immunocompromised host, it is greatly affected and
16 depressed; therefore, there isn't the normal ability of the
17 host to remove the virus from the lesion, so you have a very
18 slow clearance of the lesion. The lesions last for a much
19 longer period of time, for weeks, and if one were to apply
20 therapy, it would take a long time to get the same results
21 that it would in a normal host.
22 So you have a situation here that is perfect for a
23 resistance to develop. That is, if you have a lot of virus
24 which has the propensity every now and then to make a
25 mutation, and you grow it in the presence for a long time of

1 an antiviral agent that will select out the mutants, you
2 have a moderate possibility that in fact you will have
3 resistant virus.
4 This is quite different from my own situation,
5 where I have a strong immune system, I can clear the virus
6 rapidly--whether it is resistant or not doesn't matter--I
7 resolve my lesion in a matter of days. There is a
8 synergistic effect between the drug and my immune system,
9 and the therapy is very effective, and there is a very low
10 risk of developing resistant virus in this situation.
11 [Slide.]
12 Let's now turn to lessons we can learn from
13 epidemiology in the community, and we're going to start with
14 acyclovir, where we have the most information.
15 The acyclovir experience is relevant because it is
16 so extensive, and it has gone on so long, although there is
17 an increasing amount of information with penciclovir, and I
18 am going to present that to you.
19 The reason that it is relevant in addition follows
20 from what I have told you about the biology. Both acyclovir
21 and penciclovir have similar chemical structure. I have
22 shown you that they have very similar mechanisms. I have
23 shown you that they have approximately the same mutation
24 rate, that if you look at their DNA, the mutations occur in
25 about the same regions. They have cross-resistance--in

1 fact, they have the same clinical profile in terms of
2 efficacy in the clinic. And I am going to tell you that
3 they both have the same low prevalence of resistance.
4 The surveys for resistance with acyclovir show
5 once again that resistant mutants were present before there
6 was any drug; this is a naturally-occurring phenomenon.
7 They show that there is a stable and low level of mutation
8 in the community--but I think the operative word here is
9 "stable"--and there hasn't been any change in spite of
10 greatly increased usage. The usage, you might think of
11 because we do so many more transplants nowadays with
12 immunosuppression, we have had the HIV epidemic, and we use
13 a lot of drugs as suppression in general herpes suppression.
14 In some countries, we have over-the-counter drugs that are
15 topical--since 1991 in some countries--for the treatment of
16 herpes labialis. We have topical therapy in this country,
17 actually, for genital herpes. And we have generics now in
18 many countries. So there has been a vast amount of drug use
19 which has actually shown quite dramatically here that
20 between 1987 and 1997, 1.6 million kilograms of nucleoside
21 analogs have been sold. And during this period of time, if
22 you look at the top--this is the total amount used--you will
23 see that, depending on which assay one uses for resistance--
24 this is the older assay that gave you a higher result; this
25 is currently the accepted way that resistance is measured--

1 but you see it didn't change between the pre-antiviral and
2 the post-antiviral time period. And in addition, you see
3 that using the plaque reduction assay, again there is a very
4 low prevalence over the past 20 years of resistance to these
5 drugs.
6 [Slide.]
7 The situation is the same, but different, with
8 immunocompromised hosts. I showed you data with
9 immunocompetent hosts. With immunocompromised hosts, the
10 prevalence is about 10-fold higher, but also has not changed
11 over time, depending on which type of assay one uses.
12 So the take-home message is that whether it is the
13 immunocompetent host or the immunocompromised host, there is
14 a stable and, in the first case, a low level and in the
15 second case, a little bit higher level, of resistance in the
16 community, but it has not changed.
17 [Slide.]
18 When one looks at the immunocompromised host, two
19 risk factors fall out. One is the degree of
20 immunosuppression. The more immunosuppressed an individual
21 is, the more likely they are to develop a resistant organism
22 if they are treated, and this makes sense from a previous
23 table. That means they have more virus around that is not
24 cleared, and there is more opportunity for resistance to
25 develop.

1 Similarly, the longer they are treated and the
2 longer the selection pressure of the antiviral drug is
3 applied, the more likely resistance is to occur, and those
4 have been the observation.
5 Here now, we do see a correlation, although it is
6 not a perfect correlation, between the fact that an
7 individual who is immunocompromised and has a resistant
8 virus actually has trouble clearing that virus, and
9 sometime, we actually go to using a different class of
10 drugs.
11 [Slide.]
12 I can focus finally on penciclovir itself, because
13 there are a number of studies to report. There are four
14 types of studies that have been done by SmithKline Beecham.
15 The first of these was the treatment of recurrent herpes
16 labialis with topical penciclovir. This was in the
17 immunocompetent patient. The second studies were with
18 mucocutaneous herpes simplex virus in immunocompromised
19 patients in IV therapy where penciclovir was used.
20 Recurrent herpes simplex virus infections in HIV-
21 infected patients have been treated with oral famciclovir,
22 which is the pro-drug of penciclovir. And finally,
23 recurrent genital herpes, both in the normal host and in the
24 immunocompromised host, has been subjected to suppressive
25 therapy for up to a year with oral famciclovir.

1 [Slide.]

2 If I combine all those studies together--there
3 were six studies in immunocompetent patients--we see that
4 out of 1,300 isolates, there were only three isolates that
5 were resistant to penciclovir. Two of these were the result
6 of the topical therapy trial. They occurred during the
7 first day of treatment with penciclovir, and when they went
8 back and cultured the same patients in the same episodes,
9 they did not find resistant virus. The third instance in
10 the normal host occurred in a placebo recipient who was in a
11 general herpes suppression study.

12 In the 533 isolates from immunocompetent patients,
13 there was only one resistant isolate. This again occurred
14 in a placebo recipient in a suppressive study.

15 [Slide.]

16 So if I look at, on the right, penciclovir during
17 the mid-1990s, we see a prevalence of 0.2 percent resistance
18 to penciclovir. If we look at acyclovir study in the
19 contemporary period, we see basically the same prevalence of
20 resistance during that period.

21 [Slide.]

22 Focusing even further now on the topical use of
23 penciclovir, this table combines studies from two different
24 centers which I have combined because the results were the
25 same, and it is easy to present them, but overall, you see

1 that patients who had herpes labialis received topical
2 penciclovir or placebo in these numbers. And if one looks
3 at the first isolate--sensitivity--which is measured as the
4 IC-50, or basically, the amount of drug it takes to inhibit
5 virus, you get this number in the treated group, this number
6 in the placebo group--as expected, the same--but you see
7 when the last isolate obtained while the patient on therapy
8 is looked at, again, it is no different between placebo and
9 treated patients, and certainly no different between the
10 first and the last isolates on the treated patients. So
11 there was no propensity to develop resistance in that
12 setting.
13 [Slide.]
14 I want to list for you now the limitations on the
15 development of antiviral resistance in herpes labialis, and
16 I want to start with the biological factors, some of which I
17 have mentioned and some of which I am about to mention.
18 In the immunocompetent host, the duration of HSV
19 replication is short, as I told you, therefore limiting
20 opportunity for resistance to develop. The immune response
21 is promiscuous, in that it will destroy both resistant and
22 sensitive virus. The lower mutation frequency of HSV-1
23 militates against the likelihood that resistance will
24 develop.
25 The new bullet, number 4, which I haven't talked

1 about, is the probability that transmission of oral herpes
2 probably occurs in individuals more likely by way of
3 asymptomatic shedding and saliva. I can't prove that to
4 you, but I know this is true with genital herpes, and it is
5 less likely that an individual with herpes spreads it to
6 another individual when they have an obvious lesion than it
7 is when they shed virus asymptomatically--which we do, by
8 the way; about 3 or 4 percent of every month, we are
9 shedding virus in our saliva if we happen to be carriers--
10 although that kind of shedding and transmission occurs
11 without any drug pressure and therefore is unlikely to cause
12 transmission of resistant virus.
13 And finally, as Dr. Spruance mentioned to you,
14 even if resistant herpes is selected at the periphery in one
15 of my lesions, it does not go back when I have recurrent
16 disease and become latent in my ganglia--at least, that's
17 what ew believe. Again, I can't prove that to you, but it
18 seems like that is an unlikely occurrence.
19 [Slide.]
20 If we then look at what I might call physical or
21 material factors or features with denavir, I could point out
22 to you that the high levels of penciclovir are applied to a
23 very limited area, they are applied for a short duration,
24 they are applied for a specified disease. They are clearly
25 meant to be applied to the normal host, and the small tube

1 size makes it unlikely that it is going to be used very much
2 for anything else.
3 [Slide.]
4 Now, a critical part of the story is that it is
5 not ending. There is a very significant commitment at
6 SmithKline Beecham to a program to continue to study HSV
7 resistance. they have undertaken the first herpes labialis
8 surveillance programs that have ever been done--other
9 studies have dealt mostly with genital herpes--both in this
10 country and in the United Kingdom, and they support the
11 International Society for Antiviral Research, which
12 maintains a task force that studies resistance in
13 immunocompromised patients.
14 [Slide.]
15 The U.S. surveillance is national in scope; it
16 takes all comers with herpes labialis; it studies at least
17 eight regional areas that are quite separate around the
18 country. The intent is to get 2,000 herpes simplex virus
19 isolates.
20 This study was started last March, and through
21 November 20, the first 279 patients were entered. All the
22 viral isolates are going to be studied in a single center in
23 this country using established methods, and in fact, from
24 the first 279, 61 percent of the attempts resulted in a
25 virus isolate.

1 [Slide.]

2 This program is a joint endeavor of industry, of
3 the CDC and of the ISAR Task Force. Both the CDC and ISAR
4 are meant to be the independent data review group, and
5 together, they will decide on independent guidelines, and
6 specifically, they will decide issues such as the frequency
7 and intensity of monitoring and what kind of interpretation
8 to put in the results and what kind of actions to take in
9 response to those interpretations.

10 [Slide.]

11 In the UK, the surveillance is further along and
12 is also national in scope. Again, it deals with recurrent
13 herpes labialis. It is centered in private practices, again
14 spread in many areas of the UK. There were almost 1,300
15 subjects sampled. Recruitment was completed last month.
16 Again, a single center is doing the testing with
17 conventional methods. The intent is that CDC and the ISAR
18 Task Force will be the review board. I should point out
19 from the U.S. studies, the intent was to have that as a
20 baseline to study herpes labialis in a continuing fashion
21 from this point on. The only difference is that in the UK,
22 it is a baseline, but there is OTC use of acyclovir for
23 topical therapy in the UK, and it is a baseline in that
24 environment.

25 [Slide.]

1 We have some results from the UK experience.
2 There are more than 1,000 swabs to date, and 775 actually
3 yielded isolates, a little higher percentage than in this
4 country. Four hundred sixty-eight isolates have already
5 been tested with acyclovir, and you see the same low
6 prevalence, in spite of the background of drug use in that
7 country, of resistance to acyclovir.
8 [Slide.]
9 There is also an ongoing program to support
10 preclinical work that deals with HSV resistance. There are
11 in-house scientists working with academic groups both in
12 this country and in the UK to study topics such as the
13 phenotypic nature of penciclovir-resistant isolates, the
14 molecular basis for those resistance patterns, the way that
15 these resistant viruses might behave in animals and whether
16 they cause significant disease. There is a very strong
17 attempt to refine the methods for measuring antiviral
18 resistance to determine the best cell lines, the best
19 methods, and probably very importantly, what are the exact
20 break points that we can use to decide if something is
21 resistant or sensitive. We have working models now, but
22 this can be refined.
23 [Slide.]
24 Then, there is a very interesting addition of
25 mathematical modeling to this research program. The

1 mathematical modeling does more than what I have told you,
2 which is what has been done and what is being done. It
3 allows us to begin to try to think about what might happen,
4 how can we predict the impact of antiviral use on the
5 emergence and spread of resistant virus in a community.
6 Modeling, of course, has been around, and it has
7 been done with influenza, for example, as the target virus.
8 This is a virus that mutates much more frequently than
9 herpes viruses, and if you apply the drug pressure of
10 amantadine or rimantadine in that model, it would predict
11 that virus resistance will emerge very rapidly, in a matter
12 of months, and in fact that's what we observed clinically.
13 On the other hand, Dr. Blower's group has used
14 genital herpes as the target infection and oral acyclovir as
15 the antiviral selection pressure, and her model would
16 predict that resistant virus will emerge very slowly over a
17 matter of decades.
18 [Slide.]
19 Dr. Lipsitch and his group at Emory have modeled
20 recurrent herpes labialis and topical penciclovir as the
21 selection pressure, and indeed, the find that there will be
22 a change in the prevalence of resistant herpes following an
23 OTC switch according to the model. Using a pessimistic
24 scenario, it would indicate that the rate of increase is
25 very slow, that it would take approximately 60 years for the

1 prevalence to increase from is present 0.3 percent to 1.3
2 percent.
3 If you look at a more realistic model, one that I
4 consider fits with assumptions that I think are very
5 acceptable, the rate of increase is extremely slow. It will
6 take centuries to go from 0.3 to 1.3 percent.
7 So I come full circle in being convinced that the
8 switch is unlikely to impact the prevalence of resistant
9 virus. I say this because the prevalence of resistant
10 herpes simplex has remained very low and stable despite a
11 great deal of antiviral use. This statement is based
12 largely on what we know about acyclovir, but there is a
13 growing body of evidence that has been accumulated with
14 penciclovir as well.
15 I have mentioned for you the virologic, the
16 pharmacologic, and the host-immune factors which together
17 militate against antiviral resistance developing with any
18 frequency. We have the predictions of the mathematical
19 model that I told you about. And finally, ew have the
20 surveillance program which is ongoing. This will mentor my
21 conclusions, and we will find out if there is any change in
22 a timely fashion.
23 Thank you.
24 **Case of OTC Status and Conclusion**
25 **Lynn Marks, M.D.**

1 DR. MARKS: Thank you, Dr. Levin.

2 [Slide.]

3 In our remaining time, I would like to focus on
4 our rationale for OTC switch, again centering on the OTC
5 criteria, the information that we have from the label
6 comprehension and the actual use studies, which are in your
7 briefing package, the commitment that we have toward the
8 surveillance programs as well as consumer education, and
9 finally, to conclude with how we have put together the
10 benefit and risk assessments.

11 [Slide.]

12 The criteria for OTC status center around these
13 three issues: The disease must be readily self-diagnosed
14 and self-treated. The compound of interest has to have an
15 excellent safety profile and needs to have a limited
16 potential for misuse.

17 [Slide.]

18 In terms of self-diagnosis, cold sores clearly
19 have distinct and identifiable signs and symptoms.
20 Recurrences are readily recognized not only by the cold sore
21 sufferer, but by their families and their friends.

22 And there are no overlaps with serious skin
23 conditions.

24 [Slide.]

25 Self-treatment--denavir is a simple topical

1 treatment targeted to a limited area of the skin for a short
2 period of time--four days.
3 [Slide.]
4 It has an excellent safety profile, as Dr.
5 Spruance went over and again is in your briefing package,
6 ranging from formal dermal irritancy and sensitization
7 trials up to the clinical studies, with a safety profile
8 comparable with the placebo. And then, our post-marketing
9 data, with over 1.5 million exposures around the world, with
10 no serious adverse events attributable to denavir and, most
11 importantly, no unexpected adverse experiences.
12 [Slide.]
13 If we look at the wide safety margin, there are no
14 detectable blood levels of penciclovir following excess
15 usage, so even if we model at 67 times the usual daily dose,
16 it is below the limit of detection in the blood and urine.
17 There are only 15 milligrams of penciclovir, with
18 low oral bioavailability--approximately 10 percent.
19 And if you look at famvir, again, with the active
20 moiety there being penciclovir, there are over five years of
21 experience worldwide, with over 4.5 million exposures, and
22 many of those individuals have taken famvir on a daily basis
23 for the year-long suppression of recurrent genital herpes.
24 [Slide.]
25 What can we do, and what have we done to minimize

1 misuse with denavir?

2 First, we have had a total disassociation of the

3 programs--famvir, denavir. Famvir is indicated for genital

4 herpes and shingles. Denavir is indicated only for cold

5 sores.

6 The formulations are unique. Famvir is the oral

7 pro-drug, and denavir is topical only.

8 The packaging for famvir is different in color and

9 design from that of denavir, and it has a small, 1.5-gram

10 tube.

11 Education for famvir is focused on genital herpes

12 and shingles, and for denavir, has been and will be focused

13 on cold sores.

14 [Slide.]

15 How can we understand better how appropriate use

16 will be in the actual OTC environment?

17 Our approach to that has been in two forums--label

18 comprehension studies, and there have been a series of them,

19 as outlined in your document; and the actual use trial,

20 where we had very open criteria coming into the actual use

21 trial. Rather than screening people out along the way to

22 show how well they understood and didn't participate, we

23 asked critical questions about their immunocompromised

24 nature and other aspects of their health later in the

25 program to see how far into the system they would to see if

1 they would use denavir.

2 [Slide.]

3 The approach we took was two rounds of label

4 comprehension work focusing initially on the general cold

5 sore-suffering population as well as those individuals who

6 had difficulty reading. We followed that with more

7 information from those groups and expanded into the teenage

8 population as well as immunocompromised individuals.

9 We took that label and went in two parallel

10 tracks. One was to put it into an actual use trial to

11 understand what the behaviors would actually be, and also to

12 take that label and move it through further label

13 comprehension work, focusing on the immunocompromised

14 population, ranging from cancer, transplantation, HIV and

15 AIDS. Then, we took the learnings from both of those paths

16 and put together our proposed OTC label.

17 [Slide.]

18 The key learnings we had from label comprehension

19 Studies 1 and 2 is that for product purpose and directions

20 for use, the general population, low-literacy, teenagers and

21 the immunocompromised individuals understood. However, for

22 the warnings, we found that the immunocompromised wording

23 needed refinement.

24 [Slide.]

25 The purpose of the actual use trial that we put

1 together was to characterize the actual population that
2 would be using the product--not to try to come up with what
3 the demographics of the U.S. are, but rather, what are the
4 demographics of the OTC use population, and also the denavir
5 usage in terms of how people would use the product, what is
6 the safety profile in that setting, and attention to any
7 inappropriate use.
8 [Slide.]
9 Characteristics of the OTC population mimic those
10 of the pivotal clinical trials, being predominantly female,
11 a high proportion of Caucasian. There was a median of six
12 cold sores per year per person, and 60 percent of the
13 individuals presented with a cold sore at the time of entry
14 into the trial. A very small percent had used denavir
15 previously.
16 [Slide.]
17 In terms of usage, out of the more than 4,700
18 individuals who used denavir, more than 99 percent
19 understood the indication and applied denavir to the correct
20 site; 82 percent used denavir for up to five days, and
21 three-fourths of those perceived denavir as more effective
22 than their usual medication.
23 [Slide.]
24 Duration of usage centers around what the "dosing
25 and administration" section reads--that is, four days--and

1 of those individuals who used it for less than four days, in
2 general, they were associated with lesions that did not
3 persist.
4 [Slide.]
5 The safety profile--denavir was well-tolerated in
6 all the populations, and the adverse experiences were
7 consistent in nature, frequency and type with that which we
8 have seen in the clinical pivotal trials as well as in our
9 worldwide postmarketing surveillance database.
10 [Slide.]
11 Inappropriate use--we asked very broad, far
12 reaching questions. Do you have difficulty fighting
13 infections? Have you lost 10 pounds or more in the last six
14 months for an unknown reason? We asked very open, broad
15 questions, trying to capture as many individuals who might
16 have an underlying immunocompromising condition. Then, we
17 worked together to try to see what percentage of those
18 people actually had something that would cause them to be
19 immunocompromised.
20 Again, in a very conservative nature, we had 8
21 subjects with HIV and AIDS; there were no cases of
22 transplantation; and there were individuals who used oral
23 steroids.
24 So, how is it that we have gotten this far with
25 labeling language that allowed this very small percentage,

1 but can we do better?

2 [Slide.]

3 if you look at the label that was used in the

4 actual use trial, one of the learnings we had is that if you

5 use language like "If you have a weakened immune system...,"

6 or "Ask your doctor if you have difficulty fighting an

7 infection," in the day and age where HIV-infected

8 individuals are on triple antiretroviral therapies, have CD-

9 4 counts very readily available and have quantitative R&A-

10 level testing, if you ask someone with a CD-4 count of 700

11 and no detectable R&A if they have a decreased ability to

12 fight infection, they may well tell you, "No, I don't."

13 Now, whether they are right or wrong, we were

14 trying to come up with language that moved that population

15 of people who could be considered immunocompromised away

16 from the OTC environment and more toward physician

17 involvement.

18 [Slide.]

19 How could we do that effectively? We went into

20 additional rounds of label comprehension testing. The third

21 round focused on one-on-one discussions with individual who

22 were immunocompromised and what communicated effectively to

23 those individuals; and then in further testing in round

24 four.

25 [Slide.]

1 What we learned is that specific language, in our
2 opinion, is the best approach: "Do not use if you have HIV,
3 AIDS, cancer, or an organ transplant," and "Ask a doctor
4 before use if you are taking steroids."
5 [Slide.]
6 The learnings that we have--they are outlined--
7 allow us to put in the drug facts format our proposed OTC
8 label.
9 [Slide.]
10 What we learned in terms of appropriate use is
11 that this label satisfy the criteria for self-selection,
12 product use in all populations, and that it guides use in
13 the OTC setting, and that the safety profile is appropriate
14 for OTC use.
15 [Slide.]
16 I'd like to reiterate some points about our
17 ongoing commitment. We have formed a scientific partnership
18 with individuals with the Centers for Disease Control and
19 Prevention as well as the International Society for
20 Antiviral Research, the Department of Biology at Emory
21 University, which helped us with the mathematical modeling
22 that Dr. Levin spoke to, and colleagues in industry. We
23 tried to put that together prospectively, proactively, to
24 get the right people and the right minds and the right
25 institutions together to talk about the issues and

1 independently outline to us the program that is necessary to
2 make certain the biases are excluded.
3 [Slide.]
4 We have an HSV resistance program, looking at the
5 information in the UK, where there is already five years of
6 experience with topical antivirals to treat cold sores, as
7 well as a very solid baseline of information in the U.S. to
8 complement programs that we have already outlined.
9 [Slide.]
10 In terms of our commitment to consumer education,
11 we want to focus on proper use, the fact that this is indeed
12 a viral illness and therefore is contagious.
13 [Slide.]
14 Our programs have centered on and will continue to
15 center on the audience of the cold sore suffers themselves
16 and a heavier emphasis on pharmacists through a variety of
17 printed and electronic media.
18 [Slide.]
19 In conclusion, we are convinced that denavir
20 fulfills the OTC criteria; that the OTC setting will enhance
21 accessibility and that through this enhanced accessibility,
22 we can improve disease management; and that with the package
23 of information that we have put together and our commitment
24 to the scientific understanding of this disease and the
25 surveillance, it is unlikely to increase antiviral

1 resistance. And we are committed to continuing our
2 education programs.
3 [Slide.]
4 So, why are we here? Let me summarize. I started
5 off my career in academic medicine with a subspeciality in
6 infectious diseases, where I was involved in taking care of
7 and training individuals in the burn units, the intensive
8 care units, and then, my early teachings were in the
9 epidemic of HIV.
10 I don't have cold sores, so when people talk to me
11 initially about what is the big deal, why do we care about
12 this, this is not saving lives, I have very little time to
13 talk to my patients or my students about cold sores.
14 After coming to SmithKline Beecham and working in
15 the antiviral program and having the opportunity to talk to
16 people who do have cold sores inside the company, outside
17 the company, within my family, including my wife, they give
18 me a different perspective on how important cold sores are.
19 Certainly, they get through their lives, but when they are
20 getting ready to go to an important meeting or engagement,
21 it undermines their self-confidence--are you going to be
22 looking at my cold sore, or are you going to be paying
23 attention to me?
24 When the grandchildren come over for Thanksgiving
25 like they did this last week, does my wife feel comfortable

1 expectation of its usage is if it went OTC?

2 DR. MARKS: Ron, do you have that slide?

3 [Slide.]

4 DR. MARKS: This is taking a look over time from

5 1996 and projecting out what would actually happen in terms

6 of total antiviral usage. It included not only denavir, but

7 also the information that is available on zovirax ointment,

8 which is available in the U.S. In terms of the trends in

9 topical treatment, as we have had more effective oral--well,

10 we have had oral formulations in addition to acyclovir

11 itself, with acyclovir, famvir, and so on, the use of

12 topicals is decreasing over time.

13 DR. LIPSKY: But can you be specific--for denavir,

14 currently, how much is used, and how much might be used?

15 DR. MARKS: Let's have the next slide, Ron.

16 [Slide.]

17 DR. BRASS: Could you identify yourself, please?

18 DR. BOON: Certainly. I am Ron Boon, Director of

19 the Switch Program for SmithKline Beecham.

20 The information currently for denavir usage in the

21 U.S., I'm going to ask one of my colleagues from the

22 Marketing Department who hopefully will have that figure.

23 John, do you have a current figure for what we are

24 using in the U.S. currently? And then, while he's looking

25 that up, if we could have that slide back up again please

1 that we were just referring to.

2 [Slide.]

3 DR. BOON: The expected usage within the U.S.

4 would be 180 kilograms by the year 2002.

5 DR. LIPSKY: And we don't know right now--

6 obviously, this may have some pertinence if there are

7 concerns with resistance and so on--but you don't know right

8 now how many kilograms?

9 DR. BOON: Hopefully, we can find that. If you'd

10 like to move on to your next question, we can find that for

11 you.

12 DR. LIPSKY: The next question is what are your

13 refills currently? That is, w hat percent of patients who

14 are on it refill their prescriptions.

15 DR. MARKS: In the U.S., our refill rate are

16 approximately 15 percent.

17 DR. LIPSKY: Fifteen percent. That's an

18 interesting comment.

19 DR. MARKS: We have a graphic that we can show on

20 that as well, on percentage of refills.

21 DR. BOON: George, do you have the percentage of

22 refills for us, please? Come to the microphone, please.

23 DR. BRASS: Please identify yourself.

24 DR. QUESNELLE: I am George Quesnelle, VP of

25 Marketing.

1 In terms of total prescriptions a year, we have
2 approximately 40,000 to 50,000 prescriptions per month. In
3 terms of total use, about half a million tubes at 15
4 milligrams per year.
5 [Slide.]
6 DR. QUESNELLE: Here are some statistics, finally;
7 we do have the slide.
8 Total Rx's, basically launched through October,
9 were half a million, a 17 percent refill rate.
10 We also distributed stock packages of samples to
11 physicians, and there were about half a million of those.
12 We don't have an actual count on how many of those were
13 distributed to how many patients.
14 DR. LIPSKY: Thanks.
15 So, just to get some idea of exposure, if we think
16 we're going to 180 kilograms a year, right now, you are
17 manufacturing how many kilograms? Perhaps I can just do the
18 math, but I'll probably make a decimal error, and I warn my
19 students not to make those.
20 MR. COPELAND: John Copeland, SmithKline Beecham.
21 If you look at that data, half a million comes out
22 to about 8 kilos. If you take in the extra amount, we're
23 looking at taking that up maybe to 12. If you look at the
24 forecast--and we go back to the last slide--
25 [Slide.]

1 MR. COPELAND: --you can see that, as we are
2 saying, that fortunately, the use of topicals is going way
3 down; that the total forecast at the end there in the 2-gram
4 denavir is about 180 kilograms, which if you look at the
5 total antiviral usage, as Lynn referred to earlier on, it is
6 infinitesimal compared with the total weight of antivirals
7 used systemically.
8 DR. LIPSKY: Okay, but you would be predicting a
9 fairly substantial increase for this product.
10 And finally, is it my understanding that for the
11 current package insert, the only reference to
12 immunocompromised individuals is a statement that just says
13 that the effect of denavir has not been established in
14 immunocompromised patients? Is that correct?
15 DR. MARKS: I believe you are looking at the
16 prescription--
17 DR. LIPSKY: That's right--what you have, not for
18 the OTC, but for the prescription. Is that correct--
19 DR. MARKS: Yes.
20 DR. LIPSKY: --that the only statement about
21 immunocompromised individuals--I am curious, with the strong
22 emphasis on the OTC, can you explain the discordance in
23 that?
24 DR. MARKS: Yes. In terms of looking at the
25 package for Rx approval, the studies, the two large pivotal

1 trials that Dr. Spruance went through were in
2 immunocompetent individuals. Therefore, in discussions with
3 FDA at the time of approval and the labeling discussions,
4 they felt it was important to have a line in that addressed
5 whether or not there was information on immunocompromised
6 individuals with use.
7 Our program has avoided using denavir in
8 immunocompromised, and the famvir program has focused on
9 genital herpes, shingles, and immunocompromised individuals.
10 DR. LIPSKY: But at the time when that drug was
11 introduced, there was never a concern about its use to the
12 point that the label would make, at least to physicians,
13 some comment about the immune status of the patient?
14 DR. MARKS: The agreement that we had with FDA in
15 terms of the labeling was in terms of communicating
16 information to physicians, informing them that there was no
17 information in the immunocompromised population, was how
18 they felt we should go.
19 DR. BRASS: If I could just interrupt for a
20 second, particularly for those members on the panel who are
21 from the Antiviral or consultants, issues that come up
22 during switches, we try to focus only on those that are
23 relevant to the OTC use and we try not to go back except as
24 they are relevant to the current decisionmaking.
25 DR. LIPSKY: Well, I think it is interesting that

1 there is a tremendous emphasis for the patients not to take
2 it--yes, Heidi--whereas there is not one, single reference
3 to that concern for the physicians.
4 Heidi, do you want to clarify that?
5 DR. JOLSON: Just very briefly, I think the
6 concern with the OTC product is that a topical product may
7 not be appropriate therapy for patients who are
8 immunocompromised who have herpes simplex. I think that
9 that was more the concern, and that is why there is less
10 focus on it in the prescription label, where it is assumed
11 that the individual physician will appropriately tailor
12 therapy, so the label would just point out that the product
13 has not been studied in immunocompromised; but the plan
14 would be that there would need to be much more focus in an
15 OTC product, because in fact systemic therapy, oral therapy,
16 may be indicated for those individuals.
17 DR. BRASS: Other comments?
18 Dr. Masur?
19 DR. MASUR: You made an interesting comment at the
20 end about viral transmission. You have a lot of data on
21 viral shedding. Is there in fact data showing that the use
22 of this product will decrease transmission?
23 DR. MARKS: No. In terms of direct information on
24 transmission, that is, as I am sure you know, in terms of
25 genital herpes, where it has best been studied, the ability

1 in that area is under discussion, and with cold sores, we
2 believe that the treatment is applied during the time when
3 cold sores occur, and as Dr. Levin discussed, that may well
4 not be the actual time when people are coming into greatest
5 contact. So from that standpoint and the fact that it is an
6 antiviral, we can put together a theoretical discussion
7 talking about having an impact on decreasing viral shedding
8 and antiviral activity that is local, education about the
9 fact that this is a viral disease in an area where most
10 people don't understand that--that we can have those impacts
11 as we move down the road.
12 But if you are talking about direct clinical
13 evidence of matching people up and seeing if they can shed
14 virus, that information is not available.
15 DR. BRASS: Yes?
16 DR. KODA-KIMBLE: Perhaps you or Dr. Spruance can
17 answer this question. In the actual use trials, I believe
18 patients did not use it every two hours, or they seemed to
19 use it for a median of four times a day.
20 Do you have any evidence of efficacy with that
21 kind of use, and what was the actual use in the clinical
22 trials?
23 DR. MARKS: Yes, that is an important question,
24 and the answer is we do have information on that. In our
25 actual use trial, we purposely tried not to intervene to

1 coax individuals into using the product in any way, but
2 rather to step back and see how they dose. In that, you
3 could see that there was roughly five-times-a-day usage in
4 the actual use trial, and there was a little bit better than
5 that, around six to seven times a day or so, in the pivotal
6 clinical trials.
7 So we have looked at the efficacy information from
8 that in a couple of ways, and I am sure Ron will be happy to
9 show us that data.
10 [Slide.]
11 DR. MARKS: Here, we are looking at the average
12 duration of critical lesion stages, and again, not to try to
13 confuse people, critical lesion stage is the FDA-preferred
14 approach in terms of understanding the disease process. So
15 if we look at that from both of our pivotal studies
16 combined, 024 and 025--and again, they were conducted very
17 similarly, with the same entry criteria, the same
18 methodology in order to facilitate combining the data--if we
19 look at more than six applications per day, or whether we
20 look at greater than four applications a day, if we look at
21 024 and 025, you can see we have efficacy that is very
22 similar to that which is described in the information
23 already and that again attained statistical significance.
24 DR. BRASS: Dr. Krenzelok?
25 DR. KRENZELOK: I have three very brief questions,

1 Dr. Marks. Number one, what do you anticipate the cost to
2 the consumer will be for the product if it is available OTC?
3 DR. BRASS: Again, in general, that is not an
4 issue that the Committee goes into--you can answer if you'd
5 like to, but in general, it's not an issue we go into.
6 DR. MARKS: I can pause and try to be helpful. In
7 terms of cost, especially if you take into consideration
8 access to a physician, the visit, copays, pharmacy, the
9 whole package of information that is available on that, we
10 believe it will be less expensive in the OTC environment.
11 DR. KRENZELOK: On the issue of testing in the
12 low-literacy population, I know that in Western
13 Pennsylvania, they have done some studies that we have done
14 that have looked at the illiterate, and allegedly about 20
15 percent of the population of Western Pennsylvania is
16 illiterate, meaning they have a second grade reading level
17 or below.
18 Did you really look at this in the illiterate
19 population, or was it just in the seventh and eighth grade-
20 level population that it indicated in the materials?
21 DR. MARKS: We did not look at the illiterate
22 population. The information we have is based on the
23 literacy levels that you are describing with a sixth/seventh
24 grade education, which is our standard approach to label
25 comprehension. Regardless of class of compound, we look to

1 low-literacy individuals as opposed to the individual who
2 cannot read.
3 DR. KRENZELOK: A final question--you mentioned in
4 the literature that if you are breast-feeding or pregnant,
5 you should consult your physician, and it also mentions if
6 you have swallowed some of this, you should call your health
7 care provider or poison center. Being on the other end of
8 that situation--I know we have never received any material
9 from the company as to what we might consider doing--have
10 you considered, rather than using this in default to talk to
11 your consider, giving them so information so they can be a
12 bit more proactive in making these decisions about breast-
13 feeding and pregnant women, because I think we have put so
14 much reliance on what we think they might know, but do they
15 really have a good background in that information.
16 DR. MARKS: I think there are a couple of
17 approaches to that that we can work with the agency on in
18 terms of how to best do it, but one of the things that is
19 already available in the proposed label is an 800 number.
20 That is not just limited to the consumer who might want to
21 call in with a question, but also the professional could
22 call in with a question. If they identify themselves as
23 seeking information, we can get information and discuss
24 that.
25 We try not to tell people how to practice

1 medicine; what we try to do is give them the information
2 that is available in terms of making the decisions that are
3 important for that patient and that individual.
4 So in terms of how much information is in there,
5 how we can provide that, we are very open, especially in
6 these days of internet access, to discussions with opinion
7 leaders and experts in the field, the agency itself, in
8 terms of how best to educate consumers on those issues.
9 DR. KRENZELOK: Thank you.
10 DR. BRASS: Dr. El-Sadr?
11 DR. EL-SADR: You showed that the topical market
12 is very small in proportion to the oral market. I am
13 wondering if you know what proportion of patients who do
14 have herpes labialis are prescribed oral medications rather
15 than topical medications--in the immunocompetent population.
16 DR. MARKS: I honestly don't know the number, but
17 I can give you sort of a breakdown of percentages of how
18 that flows. If you look at the 25 or so percent that
19 actually go to a physician, 45 percent of those who talk to
20 their doctor about it get a prescription, and it is the
21 minority who get a prescription for topical products; it is,
22 classically, an oral formulation that they are given a
23 prescription for. I don't know the exact breakdown in terms
24 of that percentage.
25 DR. BRASS: Dr. Yogev?

1 DR. YOGEV: I have two questions. One, do we have
2 any data of using in vitro lower concentration of your drug
3 to see what percentage of resistance will develop?
4 DR. MARKS: I apologize. I couldn't hear the
5 question.
6 DR. YOGEV: If you put a lower level of the drug
7 in vitro in the same mechanism that we just heard .1 or .3
8 will develop resistance, would you get an increase in
9 resistance? Was that done a lower level of the drug, a
10 different, lower level?
11 DR. MARKS: No. I think I am understanding your
12 question. If we use low levels of drug in vitro, do we see
13 a difference in the rates at which resistance increase? The
14 short answer to that is that when you do that, it does not,
15 and the long answer, I am happy for Dr. Leary, who is in our
16 Virology group, to address.
17 DR. LEARY: Yes. If I understand your question
18 correctly, you are asking whether low concentrations in
19 vitro are more likely to generate resistance than high
20 concentrations. We have done in vitro selection of
21 resistant mutants at several different concentrations, and
22 the bottom line is at any concentration that you can select
23 resistant mutants, and there doesn't seem to be an advantage
24 to going for a lower concentration, the resistant mutants
25 are there, as Dr. Levin showed. And I think we may have

1 some data talking about our in vitro selection.

2 [Slide.]

3 DR. LEARY: Basically, in this set, we have looked

4 at both HSV-1 and HSV-2 mutants that were selected either

5 for penciclovir or acyclovir, and we see no difference in

6 the ability to select resistant mutants with either one.

7 DR. YOGEV: The question is if you put a lower

8 level, did you get a higher percentage of this selection?

9 DR. LEARY: The answer to that is no.

10 DR. YOGEV: Because there was no presentation of

11 those data. So you did try to put very low level?

12 DR. LEARY: Yes.

13 DR. YOGEV: And second, I was wondering--I didn't

14 see anything in your program at all to make this drug

15 available to children. You can rest assured that if it will

16 work on the parents, or if that is their impression, it is

17 going to be used on children, and there are no data and no

18 claims. Do you have any plans for this?

19 DR. MARKS: Actually, when we put together the

20 actual use trial, the entry criteria into that study was 12

21 and above. So in terms of generating information on how it

22 would be used in the population to address that issue, they

23 were included. And we are in discussions with FDA regarding

24 the labeling in terms of age to decrease that through

25 information that we are putting together with their

1 cooperation.

2 DR. BRASS: Dr. Laughlin?

3 DR. LAUGHLIN: Over-the-counter usage has already

4 been approved in a number of countries, and most of it is

5 pharmacist-regulated. There are a few countries like the

6 U.S. where approval was patient-selected, self-selected.

7 New Zealand was one of those countries, and I understand it

8 has been just a little over a year since you received

9 approval, but I did notice that New Zealand was not among

10 the list of UK countries that the ISAR study was going to

11 look for resistance in. Do you plan to do that, and also,

12 do you have any data on who is actually buying and using the

13 compound in New Zealand? The label restricts it to over 18,

14 but it would seem fairly simple for a younger person to buy

15 it.

16 DR. MARKS: You are correct in terms of our

17 program not focusing on the use in New Zealand. Again, we

18 were establishing a baseline in the UK where penciclovir is

19 not available over-the-counter yet, or without a

20 prescription. In New Zealand, we haven't done that, because

21 it is already in that environment.

22 We have access to getting isolates in those areas,

23 and in our discussions with ISAR and Centers for Disease

24 Control, we have the capability to do that if the

25 independent group feels that that is important.

1 In terms of obtaining information from those
2 individuals, they are part of our post-marketing
3 surveillance. We have offices there; we do have a pharmaco-
4 vigilance program in New Zealand, so we do capture the
5 adverse event data from New Zealand.
6 MR. COPELAND: Just to add to that, we are very
7 interested in fact in looking at that, because you are quite
8 right, there is a slightly different situation than we find
9 in the rest of the world. The problem we have is a) the
10 location, but b) the absolutely very, very small amount of
11 usage in that particular situation. This is something that
12 we'll have to look at, but I must tell you that when we are
13 looking at the amount of kilograms used in the U.S., you'd
14 have to be looking at spoonsful with regard to New Zealand.
15 DR. BRASS: Thank you.
16 Dr. McKinley-Grant?
17 DR. McKINLEY-GRANT: I am Dr. McKinley-Grant, and
18 I am a dermatologist practicing in Washington, D.C.
19 Actually, in dermatology, we do see a large number of
20 patients with herpes labialis. People find that it is an
21 important thing to come to the physician for, and, maybe
22 because it is Washington, but we have to have very rapid
23 resolution, and therefore, ew usually use oral antivirals.
24 My question, though, is that years ago, when
25 acyclovir first came out as an ointment, there was the

1 report of the resistance, and that is why many physicians
2 have gone to using the oral antivirals. I was just
3 wondering in the data that was presented for the resistance
4 if that included oral and topical penciclovir and acyclovir,
5 or was it primarily just topical?
6 DR. MARKS: The data that we have on antiviral
7 resistance ranges across our program, and in terms of the
8 penciclovir studies, that is with oral drug, topical drug,
9 cold sores, genital herpes, normal hosts and
10 immunocompromised hosts; so it is ranging across that.
11 The epidemiology studies that Dr. Levin showed are
12 again regardless of usage patter, predominantly oral usage,
13 I am sure--or intravenous, in some of the first, because
14 that's when acyclovir was introduced heavily with the
15 intravenous formulation for immunocompromised individuals,
16 so the epidemiology focused on that. So regardless of where
17 we look, there has been a stable rate and a low rate of
18 resistance despite escalating tonnage use over the last 15
19 years.
20 DR. BRASS: Dr. Woolson?
21 DR. WOOLSON: Since you have noted that a number
22 of people experience this six or eight times a year, so
23 individuals will likely be using this medication, if it is
24 approved for over-the-counter use on multiple occasions, I
25 was wondering if the clinical effect that you have seen, the

1 one-half day in shorter duration--was there any relationship
2 of that to the amount of repeated use? Is there any
3 longitudinal type of data analysis that you have undertaken
4 to see whether individuals who use this repeatedly have a
5 diminished clinical effect?
6 DR. MARKS: When ew talk to individuals about
7 whether denavir works, if you ask them, there is no effect
8 over time when we have discussion on them. We do have
9 information ongoing to try to capture information on repeat
10 use. We have experience on repeat use from the prescription
11 environment and also from the two databases that are
12 outlined in the safety section of the briefing document, the
13 GPRD and the MediPlus databases which are available in the
14 UK. We have repeat use information from that from a safety
15 perspective, but we have had no reports about decreased
16 efficacy with repeated usage.
17 DR. BRASS: And no studies to address that
18 question?
19 DR. MARKS: There are no studies that we have done
20 to date that ask that question.
21 DR. BRASS: Yes?
22 DR. DIAZ: You mentioned that there are a number
23 of countries where it has been used over-the-counter, some
24 as long as from 1991. Do you have any post-marketing
25 surveillance or information about the average number of uses

1 per year and the range and likewise, the accuracy of usage,
2 and if there is any antiviral resistance data from multiple
3 users?
4 DR. MARKS: The antiviral resistance data for
5 multiple users is indeed probably captured in that, and when
6 we get background information about whether you have used
7 antiviral compounds before, it is quite common for the
8 response to be yes, and it can be a variety of antivirals,
9 both topical and oral, all mixed into that. Teased out
10 separately, it is not quite that simple, since they use more
11 than one compound. It is hard to get a pure population of
12 individuals who use just one type always. And I believe I
13 missed the first part of the question.
14 DR. DIAZ: If you have any data, especially in
15 other countries where it has been licensed for a long time
16 over-the-counter, of average number of uses per year by
17 individuals and the accuracy with which they use it.
18 DR. MARKS: I believe John Copeland can help us
19 with that.
20 MR. COPELAND: It's nice when people give you a
21 note just as you come up. I was going to give any answer
22 anyway. Perhaps the best way of looking at this is that if
23 you look at some of the best companies, like Germany and the
24 UK--and I mean "best" in terms of 1993 in time--basically,
25 what we are seeing is that because, as we have seen this

1 morning, sufferers do not go to doctors, what you found was
2 that anywhere between only 4 percent and a maximum of 11
3 percent of sufferers--that is 4 to 11 percent of the 20-odd
4 percent people who suffer--ever went to a doctor. Once it
5 became OTC, the most maximum figure even after five years
6 went up to about 55 percent.
7 So yes, the usage did go up, but that tended to
8 prove the fact that availability was quite important to the
9 sufferer.
10 In terms of the number of tubes that are being
11 used, we have some data, but basically, you could say that
12 we were quoting earlier on about a sufferer buying one tube
13 per year; I have seen some data in Europe which would
14 suggest one to one and one-half tubes per year.
15 DR. BRASS: Dr. Laughlin?
16 DR. LAUGHLIN: Despite the small size of the tube,
17 I imagine the most common misuse of the product will be for
18 topical application to genital herpes. Do you have any data
19 on either safety or efficacy for genital herpes itself, or
20 mucous membranes, either?
21 DR. MARKS: In terms of the safety profile, the
22 experience has been centered on the oral cavity, and in
23 terms of the safety there, it is very comparable to placebo.
24 There is on reason to suspect that it would have a different
25 safety profile in the genital region, but our development

1 has not been in that direction so we don't have any efficacy
2 data on genital herpes with denavir and no large amount of
3 data other than the occasional report that we hear of misuse
4 for topical products in that region.
5 DR. BRASS: Go ahead.
6 DR. LAUGHLIN: I guess Dr. Marks mentioned the
7 fear of kissing earlier. I have a comment on the education
8 package. I think it mentioned that people should be careful
9 not to kiss other people. I think that what was implied was
10 that transmission of oral herpes was the likely consequence.
11 I imagine you should also mention the possibility of
12 transmission of genital herpes and also the danger of
13 serious illness in newborns.
14 DR. MARKS: Great points. In our educational
15 program, we are trying to work with experts from a variety
16 of places and plan to work closely with the agency in terms
17 of trying to make sure we get the key messages across.
18 Again, we have the opportunity to educate
19 individuals in a variety of formats--one, unbranded material
20 educating about herpes infections, which we do and will
21 continue to do; famvir-specific information regarding
22 genital herpes, and also the denavir program, to give
23 information.
24 There is a fine line between trying to tell people
25 what it is for rather than outlining all the things you

1 could possibly not use it for and putting that in your mind.
2 So working with the agency and with experts to effectively
3 communicate messages about herpes diseases is tantamount to
4 what we are doing.
5 DR. BRASS: Dr. Olivo?
6 DR. OLIVO: I wonder if you could comment on some
7 of the concerns I have about resistance, specifically, the
8 technical aspects of monitoring resistance. It is my
9 impression that the assays that are used underestimate the
10 prevalence of resistance because the assays look at the
11 population in the isolate rather than individual viruses, so
12 for instance, you could in your assay have a one percent
13 resistant virus in the general population that is being
14 assayed, and it would score as sensitive. You could have
15 ten times that, 10 percent resistant in the population, and
16 it would still score as sensitive, because you are looking
17 at--plaque reduction assay, whatever the assay is--the
18 population's response to the antiviral in vitro.
19 So I am concerned that the way the monitoring is
20 being done, for technical reasons, it is underestimating the
21 prevalence of resistance, and a large increase could occur
22 in the general population, and we would not see it.
23 DR. MARKS: Right. Before I ask Dr. leary to
24 comment on the specific detail of the virology, that is the
25 reason why we're putting together proactively the

1 individuals and the institutions that we have described, is
2 to go through those issues and make certain we've got the
3 program together that will address those issues.
4 I will ask Dr. Leary from our Virology group to
5 comment.
6 DR. LEARY: Yes, I'd like to comment on the
7 sensitivity issue. I think we share your concern that the
8 plaque reduction assay may not be able to look at these
9 sorts of minute trends in the population of virus in this
10 individual sample, for example. The problem is there is no
11 alternative that is better, and we did not come up with a
12 plaque reduction assay as a method for monitoring resistance
13 on our own; that's based on conversations with the ISAR Task
14 Force and other experts in the field. There really is on
15 other proven way of monitoring resistance prevalence.
16 I think that what we are both looking at is that
17 there is a difference between what proportion of resistant
18 viruses might be in any sample of a culture, and what the
19 prevalence of resistant isolates--in other words, where the
20 prevalence is high in that sample--they are two different
21 questions. So things like plaque autoradiography, which I
22 suspect you are thinking about, answer one question, but
23 they don't follow clinical resistance, which is correlated
24 with plaque reduction assay results.
25 However, if there were a more sensitive technique,

1 we would be delighted to consider that, and in fact, we are
2 working to try to develop those.
3 I hope that helps.
4 DR. OLIVO: It does answer my question, but it
5 brings up the point that I am trying to make, which is that
6 perhaps we don't have the technical ability right now to see
7 a large trend in the fraction of resistant viruses in a
8 particular patient, and the impact that that could have in
9 terms of transmission of resistant virus to other patients
10 and even on that patient.
11 Another related question I have is on the issue of
12 immunocompetent versus immunocompromised. The
13 immunocompromised patient population comes from the
14 immunocompetent--people get AIDS, people get transplanted.
15 The pathogenesis of the virus allows resistant virus to
16 establish latency. If you have a mixed population, that TK-
17 minus or TK-deficient virus can reactivate in the context of
18 complementing wild-type virus. Then, if the fraction of
19 latent virus that is resistant is higher, and that patient
20 becomes immunocompromised, he now has a much greater
21 likelihood of having drug-resistant virus to deal with when
22 he is immunocompromised.
23 I'd like you to comment on that scenario.
24 DR. LEARY: Yes, I guess that is a logical
25 scenario. The problem is that transmission of resistant

1 virus is basically not known in the human population, with
2 one exception, and that is the cost article, and that is not
3 proven. So the transmission issue is hard to support based
4 on clinical data.
5 Maybe you can remind me again about the second
6 point you are trying to make in terms of evolution within
7 the patient, talking about acquired resistance.
8 DR. OLIVO: Yes. I am talking about the problem
9 of if the prevalence in a patient, or the percentage of the
10 patient's virus is increased in terms of resistant virus,
11 and he establishes latency with that virus and then
12 reactivates at a time when he is immunocompromised, he has a
13 greater problem to deal with.
14 In other words, I am making the point that this is
15 not a hard and fast line between immunocompromised and
16 immunocompetent, and because the virus establishes latency
17 and can reactivate, and despite the fact that TK-deficient
18 or TK-minus viruses are thought not to reactivate
19 efficiently, they can in the context of a mixed population.
20 So there is reactivation with TK-minus or TK-deficient virus
21 in the population of wild-type.
22 So if the worst case scenario is that denavir will
23 increase the fraction of resistant virus in the population,
24 we are going to see this in our 10-year-later
25 immunocompromised patients.

1 DR. MARKS: This is one of those topics that we've
2 got more people who are ready to answer, so I am going to
3 try to take this because it is a very important point, and
4 we want to treat it correctly.
5 I will start by having Dr. Levin respond in terms
6 of some of the issues we have, and we also have information-
7 -in the mathematical modeling, those are assumptions and
8 discussions that are in that, and we would be happy to
9 expand upon those as well.
10 DR. LEVIN: One of the issues or scenarios you
11 brought pu, I think, was the possibility that resistant
12 virus would develop at the periphery and then become latent
13 in a normal host who then becomes an immunocompromised
14 patient.
15 But we think that that is probably only going to
16 happen if you happen to have your resistance as part of a
17 primary episode. We think you seed your ganglia with latent
18 virus when you first get infected and that if you are a
19 normal host, you don't keep reseeding from subsequent
20 recurrences.
21 Denavir is meant to be applied to recurrent herpes
22 labialis, and is very unlikely to be used with primary
23 disease, or is not meant to be used with primary disease.
24 So I think the likelihood that it will be applied to many
25 people with primary infection and therefore resistance

1 develop because of it and then become latent in the pool of
2 human beings who are normal is unlikely.
3 Do I have your question right, and does that help
4 somewhat?
5 DR. OLIVO: Well, it is all predicated upon an
6 assumption which I don't think is unreasonable that you are
7 making, and that is that you do not reestablish when you
8 reactivate.
9 DR. LEVIN: That may happen in the
10 immunocompromised patient that you can get what is called
11 acquired resistance, but as Dr. Marks mentioned, that is
12 build into the mathematical model, and perhaps we can talk
13 about the role that that will play as well.
14 DR. MARKS: Dr. Lipsitch is from Emory University,
15 and we have given an educational grant to that group to look
16 at mathematical modeling. He can walk us through some of
17 the key assumptions.
18 DR. LIPSITCH: Would you like me to give you the
19 full story of the model, which is about 10 minutes, or would
20 you like just the acquired resistance piece?
21 DR. BRASS: The acquired resistance.
22 [Laughter.]
23 DR. LIPSITCH: Just the acquired resistance; okay.
24 That is Slide 9.
25 [Slide.]

1 DR. LIPSITCH: One of the reasons for doing
2 mathematical modeling is to consider the possibilities, like
3 the ones you have described, where there is not clear data
4 answering exactly what the particular rates are, but we
5 think that we can incorporate the bearing levels or possible
6 levels of the parameters into the question of acquired
7 resistance and then calculate a rate at which that
8 resistance increases.
9 If you look at this slide, when you model the rate
10 of increase in resistance--strictly acquired resistance,
11 meaning resistance in individuals who have been treated and
12 develop resistance as a result of that treatment--if that
13 occurs, the rate at which it increases is the product of
14 four factors. One is the level of treatment, multiplied by
15 the probability that resistance appears in a treated
16 individual, multiplied by the probability that that
17 resistance persists in that individual rather than being
18 just a transient as it certainly is in some cases,
19 multiplied by the number of cold sores a year, because that
20 factors into how many people are treated, or how many
21 treatments there are.
22 As you see from this slide, there is a lot of
23 uncertainty in some of those parameters, and that comes out
24 as uncertainty in the predictions, but it is uncertainty
25 within a range, and let me try to explain where we think

1 that range may be reasonable and which parts are extreme.

2 The first question is percentage of cold sores

3 treated. Thirty percent is SmithKline Beecham's optimistic

4 prediction based on some data from the UK of OTC

5 availability and other factors, and it could be as high as

6 30 percent, or it may be less percentage of cold sores

7 treated.

8 The probability of the resistance appears in

9 treated hosts. The most relevant data for that are from 171

10 isolates in which individuals who are looked at by SB to see

11 whether, upon treatment with penciclovir of a single

12 episode, there was a change in the IC-50; and in none of

13 those people did resistance appear.

14 If you take the point estimate zero out of 171,

15 that is zero, but given the sample size, you can calculate a

16 confidence interval, and the upper end of the 95 percent

17 confidence interval for that is 1.8 percent, so that is kind

18 of the upper bound that we have used for that figure.

19 Next is the probability that resistance is

20 permanent, and that really depends on this question of the

21 roundtrip hypothesis and whether the selected viruses can go

22 back and repopulate. In that case, we really, again, are

23 uncertain. It is known to be very improbable, but how

24 improbable is unclear, and I'll explain where we got the

25 final numbers in a minute.

1 Number of cold sores per year that we used in this
2 calculation is two to three. That averages over those
3 individuals who have no cold sores per year and who would
4 not treat, so that is why it is a bit lower than some of the
5 other numbers you have seen.
6 When you multiply those together and calculate the
7 rate, you can then find out what is the time until there is
8 a one percent increase in the prevalence of resistance in
9 the HSV-1 population. And the number one percent was chosen
10 because it is a number that is reasonably easy to detect in
11 a sample--a sample of a reasonable number of individuals in
12 the community. It is not necessarily a clinically relevant
13 number, but it is a number that was detectable and small, so
14 that is how we chose that number.
15 You see that given these uncertainties, you go, in
16 a very optimistic scenario from 40,000 years down to a
17 pessimistic scenario of 60 years, and the bottom line is
18 data that is not in the original briefing document that went
19 to FDA. The reason for including that was that very
20 recently we became aware of the UK data from some
21 surveillance where OTC acyclovir has been available for five
22 years, and based on that data and the observation of
23 apparently no change, or at least no detectable change, in
24 the levels of resistance, we then again, taking into account
25 sample size and confidence intervals, said, well, what is

1 the upper limit based on that of how fast resistance could
2 be arising given that we don't see any resistance arising,
3 and that is this 12 year figure.
4 So that is taking rather extreme biological and
5 other values and also the upper end of the confidence limit
6 from the UK data.
7 Could I have the next slide, please?
8 [Slide.]
9 DR. LIPSITCH: So, just to summarize that, there
10 is uncertainty about the parameter values, and that bottom
11 line there is using the newest data that we have available
12 to show what the upper bound on the uncertainty is. We
13 think the other lines of the table are more likely, because
14 that worst estimate combines all the worst assumptions
15 happening together.
16 As you point out, all the existing data is limited
17 by the fact that it is a plaque reduction assay that only
18 look at the majority of the population, and so that is kind
19 of a caveat to our predictive ability based on the model,
20 that if it is occurring slowly within individuals, that
21 wouldn't be picked up by the plaque reduction assay, and
22 therefore, we can't put numbers into the model from that.
23 What could be done is a repeat use trial that
24 would begin to address that problem.
25 DR. MARKS: So let me take a stab at summarizing.

1 if we look at the past 15 years or more in terms of
2 escalating antiviral use, and we try to understand why it
3 is, based on the biology of the disease process, why
4 resistance rates are unchanged in that time, and then we
5 take that information that is available and take the worst
6 case caveats and try to put them into models from what is
7 known, and again, taking the worst aspects of that, when you
8 take the reality of that, our bottom line is we believe that
9 in order to go from a one percent instance, if you take
10 those case scenarios, between 60 and 200 years is where most
11 of us net out in terms of trying to understand what the
12 implications are.
13 DR. BRASS: Go ahead, Dr. Olivo.
14 DR. OLIVO: Just a follow-up question. Would you
15 expect in the mathematical modeling that the percentage
16 resistance in the immunocompromised ratio would be
17 maintained, so that when you are talking about a one percent
18 increase in immunocompetent, that would be a proportional
19 increase in immunocompromised?
20 DR. MARKS: Dr. Lipsitch, again.
21 DR. LIPSITCH: Yes. Essentially, we expect a
22 similar trend to continue in that way. If there were such
23 an increase, it would have to be through the mechanism you
24 suggested earlier, that people are treated when
25 immunocompetent, become resistant if that happens, and then

1 become immunocompromised. The transition part of the model
2 which I didn't just talk about--everything happens much more
3 slowly than what we have just described, or at least more
4 slowly and in many cases much more slowly. So that part, we
5 sort of think is very clear. It is really through acquired
6 resistance that either group would be--if anything happens,
7 it would be through acquired resistance for either group.
8 DR. BRASS: Dr. Sachs?
9 DR. SACHS: You do make one assumption about the
10 rate of permanent resistance being only as much as 5
11 percent, that 95 percent of people who became resistant
12 would resume not being resistant, I guess. Is that correct?
13 DR. LIPSITCH: That's correct.
14 DR. SACHS: And one question about safety. Is
15 there any information about accidental exposure to the eye,
16 where I think it is very likely. I know you talked about
17 the mouth and ingestion.
18 DR. MARKS: Actually, in terms of the eye, we have
19 animal work that says it is mildly irritating to the eye,
20 and we say avoid use in and around the eye; but in terms of
21 our safety profile, that actually doesn't show up in our
22 safety database worldwide. We have had no report of anyone
23 who has actually done that.
24 DR. BRASS: Dr. Feinberg?
25 DR. FEINBERG: Can you compare for us the relative

1 efficacy in terms of median shortening of lesion for topical
2 and oral drug, if that data is available?
3 DR. MARKS: I'd love to if you'll give me a little
4 poetic license where it requires me to extrapolate from the
5 information. Again, head-to-head comparison trials where we
6 look at oral dosing with the placebo versus oral dosing with
7 an active, if we try to take that and compare it purely to
8 denavir, the information we have from that is in a recently
9 completed study which looks at a treated versus untreated
10 population. The outline of that was in your briefing
11 document in terms of putting together a pilot study. From
12 the pilot study, we moved on into a large-scale study, and
13 I'll be happy to show you that information.
14 [Slide.]
15 DR. MARKS: This was a blinded, placebo control,
16 multicenter study to evaluate efficacy and safety of
17 penciclovir, denavir, creme, in terms of sun-induced herpes
18 labialis. This was natural, sunlight-induced cold sores in
19 individuals who spent their time by a swimming pool, and
20 when they had lesions, we put them into the study.
21 [Slide.]
22 They had a history of sun-induced herpes labialis
23 with at least three recurrences a year, and this minimal
24 erythematous dose, for those of you familiar with UV
25 reactivation models which Dr. Spruance is heavily involved

1 in in terms of the literature--what we do is try to
2 understand how much sunlight exposure would be necessary to
3 induce a cold sore by understanding how much causes
4 erythema.
5 They were exposed to sunlight at a multiple of
6 that dose and then randomized to receive either penciclovir
7 creme or purified water which was in a little plastic tube
8 so the water had a smell to it of plastic as opposed to in a
9 cup or something like that, trying to blind them to it.
10 then, both groups were given an oral placebo tablet. In the
11 informed consent, they were told they would either get an
12 active compound or a placebo; they were not led to believe
13 that the active would be in the oral or the topical or any
14 permutation of that, trying to cause no bias in the program.
15 [Slide.]
16 And in terms of the individual who dispensed the
17 medication, they were separate from the physicians who
18 reviewed the data on terms of how their cold sores were
19 healing. The patients were kept separate from each other so
20 they could not discuss what treatment options they were on.
21 [Slide.]
22 The treatment was supplied within an hour at the
23 papule stage--when they first got a bump--not to be confused
24 with a tingle, because it might have been sunburn, or
25 redness, because again it might have been sunburn. So they

1 started at the first critical lesion stage and applied every
2 two hours for four days.
3 [Slide.]
4 In terms of lesion healing, we looked at that from
5 classic ways of analysis--time to healing, duration of the
6 lesion, and durations of the individual lesion stages, and
7 we looked at all lesions, those which are primary-delayed
8 and those which have been called immediate lesions, i.e,
9 those that come up within the first 48 hours after sun
10 exposure.
11 [Slide.]
12 We also looked at other aspects of this disease
13 that were very important to the individual who has a cold
14 sore--how large is the lesion; the pain associated with it;
15 the symptoms associated, and then, their subjective
16 assessment of how effective it worked compare to it, both
17 from an investigator point of view and from a patient point
18 of view.
19 [Slide.]
20 We had 1,175 individuals who entered the study.
21 There were 544 equally distributed across the two treatment
22 groups who developed a lesion and then initiated therapy,
23 with 518 having completed the treatment.
24 [Slide.]
25 If we look at the information, the average time

1 was 6.6 in the denavir group as opposed to 7.8 in the
2 placebo group, the medians being 6 and 7, with high
3 statistical significance.
4 [Slide.]
5 If we look at primary delayed classical lesions,
6 or immediate lesions, which have been discussed in the
7 literature as being more or less responsive to therapy, we
8 can still see that regardless of when they had the lesions
9 within the first 48 hours--which historically have been said
10 to not be treatable or at least not be amenable to antiviral
11 therapies--we were effective in that group with similar
12 efficacious to the overall, and if we look at the people who
13 had primary delayed classical lesions, i.e., vesicles,
14 ulcers, crust, it also had impact.
15 [Slide.]
16 If we look at the duration of hard crust,
17 especially in those people who had primary delayed classical
18 lesions, again the median is two days, the mean one day,
19 with high statistical significance.
20 [Slide.]
21 In terms of lesion size, statistically significant
22 and we believe clinically important reduction in the mean
23 lesion size from 73 to 52.
24 [Slide.]
25 And if we look at time to healing, lesion size,

1 duration of pain by the investigator assessment, or ask the
2 patient how noticeable the lesion was, the amount of scab
3 and crusting, swelling, cracking, overall severity,
4 regardless of how we ask them, the whole package of
5 information trying to compare this to our experiences with
6 oral formulation, statistical significance, we believe this
7 is very similar to what you would expect and anticipate from
8 the published literature on cold sores over the years, with
9 the caveat that historically, those may well have been one-
10 sided statistics, they may have been efficacy-evaluable
11 populations. There are things that happened 10, 15 years
12 ago in terms of the literature. This is the type of
13 analysis and data that is consistent with the peer-reviewed
14 publication that Dr. Spruance put in terms of the JAMA, in
15 terms of design and analysis.
16 Our apologies to the FDA. They have not reviewed
17 this information. The trial was recently completed. This
18 is our opinion, this is our study, and just in terms of
19 trying to answer your question of how we believe we match up
20 to oral formulations, we believe denavir is very effective
21 in terms of treating cold sores.
22 DR. BRASS: Does that answer your question?
23 DR. FEINBERG: Not entirely, but I'll yield.
24 DR. BRASS: Okay. At this point, we're going to
25 take a break, and we will reconvene promptly at 11.

1 [Recess.]

2 DR. BRASS: If we could reconvene, please, the
3 discussion of the sponsor's presentation raised a number of
4 points, and I realize that we did not completely resolve or
5 even complete the discussion of many of those points, but at
6 this point, rather than continuing that discussion, I think
7 it would be productive to allow the FDA review to be
8 presented to add some focus to the issues, perhaps get some
9 of the questions resolved, and then we will have the
10 opportunity in the afternoon session, during the discussion
11 of the questions posed to the panel, to elicit additional
12 conversation with the sponsors.

13 Therefore, at this time, I would like to introduce
14 Dr. Teresa Wu, Medical Officer from the Division of
15 Antiviral Drug Products, who will begin the FDA
16 presentation.

17 **FDA Presentations**

18 **Introduction**

19 **Teresa Wu, M.D., Ph.D.**

20 DR. WU: Thank you.

21 In the next hour or so, we will make FDA's
22 presentation on this particular application.

23 [Slide.]

24 Shown in this slide are the reviewers who are
25 working on this particular application. These reviewers are

1 from three divisions. The three divisions are: Division of
2 Antiviral Drug Products, Division of OTC Drug Products, and
3 Division of Drug Marketing, Advertising and Communications.
4 Next slide, please.
5 [Slide.]
6 Our presentation will start with the regulatory
7 background for this application. Dr. Lechter will present
8 her assessment of label comprehension studies. Dr. Hu will
9 present FDA's interpretation of the actual use studies. And
10 finally, I will summarize FDA's overall assessment,
11 including OTC safety data.
12 Next slide, please.
13 [Slide.]
14 Although there has been increasing interest in
15 making OTC drugs available to the public, the number of OTC
16 antimicrobial drugs available in the United States remains
17 small. There have been no systemic antimicrobials nor
18 antiviral drugs of any formulation, whether oral or topical,
19 every approved for OTC use.
20 The approved antimicrobial drugs are the mixture
21 of three antibiotics for topical use, and tolnaftate and
22 ketoconazole for dermatophyte, and miconazole and
23 clotrimazole for candida vaginitis.
24 Next slide, please.
25 [Slide.]

1 Relevant to today's discussion was a similar joint
2 advisory committee meeting held in January of 1995 to
3 discuss the OTC switch for acyclovir tablets for treatment
4 or suppression of genital herpes. The committee did not
5 recommend approval of the switch. The decision was
6 primarily based on concerns of consumers' ability to
7 correctly diagnose the recurrent episodes of genital herpes.
8 The committee felt that granting OTC status may set an
9 undesirable precedent of an OTC use of other systematically
10 administered antimicrobial products.
11 The effect of this precedent would enhance
12 concerns with the potential for hastening the development of
13 viral resistance and the potential for limiting acyclovir
14 usefulness as a treatment for both cutaneous and life-
15 threatening herpes virus infection such as neonatal herpes
16 and herpes encephalitis.
17 Next slide, please.
18 [Slide.]
19 Next, I shall briefly describe the basis for Rx
20 approval for this product.
21 [Slide.]
22 The core of efficacy data consists of two pivotal
23 trials, Study 024 and Study 025. Study 024 was conducted in
24 the United States, and Study 025 is an international study.
25 Both studies had identical study designs. Both were

1 randomized, double-blind, placebo-controlled, patient-
2 initiated study design. The placebo used in both trials was
3 vehicle. The number of patients randomized to both trials
4 was in the neighborhood of 2,000.
5 Next slide, please.
6 [Slide.]
7 Suffice it to say that FDA's analyses were in
8 general agreement with applicant's. The one percent
9 penciclovir was associated with a modest but statistically
10 significant decrease in the duration of herpes labialis
11 lesions--about a one-half day reduction in duration. The
12 only difference in terms of methodology is that FDA and
13 applicant differed slightly in the methodology of handling
14 subjects without follow-up data.
15 Next slide, please.
16 [Slide.]
17 Next, I will summarize the safety data. In both
18 pivotal trials, the incidence and profile of adverse effects
19 were similar in both treatment groups, with headache being
20 the most common reported event, followed by application site
21 reaction. All of them were of mild degree.
22 When we combine results from all clinical studies-
23 -that is, in addition to these two pivotal trials, we added
24 some pilot studies together--the incidence of application
25 site reaction was around 2.5 percent. This number is

1 slightly higher than what was observed in the clinical
2 trials.
3 As the company presented this morning, the dermal
4 irritancy studies show that both the denavir drug product
5 and vehicle produced the same degree of irritancy, although
6 very mild. Denavir was demonstrated to have no sensitivity
7 potential, and in a guinea pig model, penciclovir was
8 demonstrated to have minimal potential for photo-
9 allergenicity.
10 It is the combination of this modest and
11 reasonable clinical benefit and a low incidence of adverse
12 events that form the basis for the prescription NDA
13 approval.
14 Next slide, please.
15 [Slide.]
16 After a little over a year marketing experience of
17 topical penciclovir, the applicant requested switching the
18 product from prescription to OTC use. During this period,
19 there have been 13 countries approved for the OTC use of
20 topical penciclovir. It should be pointed out that in 10
21 out of 13 countries, the practice of nonprescription use of
22 drug is via pharmacist intervention in contrast to self-
23 selection as is done in the U.S.
24 Therefore, in order to test the consumer's
25 comprehensibility of the labeling, under self-selection

1 conditions, the applicant provided results of label
2 comprehension studies to test how well the label was
3 understood and the results of actual use studies to all
4 comers in an environment mimicking the OTC conditions.
5 Next will be Dr. Lechter, who will present her
6 assessment of the label comprehension studies.
7 **Label Comprehension Studies**
8 **Karen Lechter, J.D., Ph.D.**
9 DR. LECHTER: Good morning. I am karen Lechter
10 with the Division of Drug Marketing, Advertising and
11 Communications, and I am going to discuss today the review
12 of the label comprehension studies conducted by the sponsor,
13 which I and Dr. Kathryn Aikin in my Division have reviewed.
14 We would also like to thank Dr. Linda Hu for her valuable
15 input into our reviews.
16 [Slide.]
17 Why do we do label comprehension studies? The
18 regulations require that OTC labeling shall be in such terms
19 as to render it likely to be read and understood by the
20 ordinary individual, including individuals of low
21 comprehension, under customary conditions of purchase and
22 use. If the label cannot be understood, the product cannot
23 be used safety and effectively in an OTC environment.
24 Therefore, these studies are conducted to
25 determine whether critical parts of the label are

1 understandable and where improvement is necessary.

2 [Slide.]

3 What is a label comprehension study?

4 The typical methodology is to recruit from several

5 geographically dispersed sites. Participants are shown a

6 carton label and are asked questions about the label

7 information. The label is usually available for reference

8 during the questioning. They may also be shown a package

9 insert and asked questions about that.

10 [Slide.]

11 They are usually asked questions about whether

12 they can use the product themselves, and they are asked

13 open-ended and closed-ended questions about what is on the

14 label. The open-ended questions are questions for which no

15 choices of answers are suggested; closed-ended questions in

16 contrast offer a choice of response, such as multiple choice

17 or yes/no questions.

18 [Slide.]

19 It is a good idea for a sponsor to conduct an

20 iterative series of studies in order to refine the label.

21 For this product, the sponsor conducted three quantitative

22 label comprehension studies and one qualitative study.

23 In a quantitative study responses are scored and

24 tabulated. Qualitative studies are not scored; they often

25 consist of discussions or interviews. Focus groups are

1 examples of qualitative studies. The results are provided
2 in terms of impressions gained from the discussion. I will
3 describe these four studies now.
4 [Slide.]
5 All label comprehension studies should be based on
6 communication objectives. For Study 1, the communication
7 objectives were self-selection and product use. The self-
8 selection objective was to communicate that consumers with
9 impaired immune systems should not use the product.
10 I'd like to note at this point that the agency is
11 still considering whether or not there should be consumers
12 who are warned not to use the product or who should consult
13 a doctor before use if denavir is approved for OTC use.
14 However, at the time these studies were conducted,
15 the sponsor assumed that certain categories of
16 immunosuppressed consumers should be so warned, and thus,
17 these warnings were tested.
18 The product use objectives dealt with these
19 warnings: Do not use in or near the eyes; stop use if you
20 have a reaction; stop if symptoms worsen or continue for
21 more than 10 days; for external use only use only on cold
22 sores; and stop use if you have a reaction to the product;
23 when to begin use, how to open the tube, frequency of use,
24 duration of treatment, and use in children.
25 [Slide.]

1 Int his study, there were 304 participants, all of
2 whom were age 18 or older. One hundred sixty-six were
3 considered low-literate--that is, they had an eighth grade
4 reading level or less, based on a commonly used literacy
5 test. They ere from six geographic areas.
6 [Slide.]
7 The procedure was that they read the carton and
8 then answered some questions with the carton present. Then
9 they read the insert and answered some questions about that.
10 [Slide.]
11 For this study, the label said "Do not use if you
12 are under the care of a doctor, because your ability to
13 fight infection is reduced (a weakened immune system)."
14 [Slide.]
15 There were some problems with the study that
16 prevented us from learning some things we were interested.
17 There were only six participants who should not have used
18 the product according to the sponsor's criteria, so we could
19 not tell how individuals who should not use the product
20 would answer questions about whether or not they could use
21 it.
22 Then, the question about self-use asked if they
23 "would" use the product rather than if they "could" use the
24 product. The result is that some responses were based on
25 non-label-related issues such as whether or not the

1 participant already had a product that they preferred.

2 The question asking whether someone with an organ

3 transplant or who is on chemotherapy can use the product

4 stated in the question that these persons have a weakened

5 immune system.

6 [Slide.]

7 Therefore, the question here read as follows:

8 "You are under a doctor's care because your immune system

9 does not work properly. For example, you are on

10 chemotherapy or are taking medicine because you had an organ

11 transplant. In this situation, would you use Denavir cream

12 to treat a cold sore or fever blister if you had one?"

13 Because this question tells a participant that

14 these persons have immune system problems, it made it much

15 easier for them to answer correctly when presented with a

16 label that stated that persons with weakened immune systems

17 should not use the product. We do not know whether they

18 would have responded correctly if they had not been told

19 that organ transplants and chemotherapy patients have immune

20 problems.

21 [Slide.]

22 So, what did we learn from Study 1? We learned

23 that a great deal of the label was understandable. More

24 than 90 percent understood the indications that fever

25 blisters are on the lips; not to use it in the genital area

1 or in or near the eyes; when to start treatment; and to stop
2 use and consult a doctor if the sore continues for more than
3 10 days.
4 [Slide.]
5 More than 80 percent understood do not use the
6 product if you have HIV; dose every 2 hours; and 70 percent
7 in the low-literate group understood this.
8 Use it for four days--72 percent in the low-
9 literate group understood this.
10 And do not use it in children--75 percent of the
11 low-literate group understood this.
12 Twenty-eight percent said they would not use it if
13 they had a cold. This is possibly due to confusion about a
14 cold sore versus a cold, and whether or not a cold weakens
15 the immune system.
16 [Slide.]
17 What do we not know from this study?
18 We don't know whether consumers understand who can
19 and cannot use the product with this particular label which
20 says: "Do not use if you are under the care of a doctor
21 because your ability to fight infection is reduced (a
22 weakened immune system)."
23 [Slide.]
24 We do not know whether consumers would understand
25 that persons with transplants and on chemotherapy have

1 weakened immune systems and should not use the product.

2 We do not know whether consumers understand what

3 conditions qualify as a "weakened immune system."

4 We do not know whether consumers who should not

5 use the product will choose not to use it.

6 [Slide.]

7 In conclusion, based on this study, there should

8 be further testing of persons who should not use the product

9 to determine if they can self-select appropriately; and this

10 was done in Study 2, which I will describe in a moment.

11 Based on Study 1, the messages that should be

12 strengthened on the label are: who should not use the

13 product; use in children, frequency and duration of use; and

14 use by persons with colds.

15 [Slide.]

16 Study 2 had the communication objectives that

17 involved self-selection issues, including: it is used for

18 fever blisters in adults; it is not for genital herpes,

19 zoster or chicken pox; immunocompromised persons should ask

20 a doctor before use; and whether the participants should use

21 the product themselves.

22 [Slide.]

23 There were 633 participants, 169 of whom were low-

24 literate. One hundred eleven were probably or possibly

25 immunosuppressed. One hundred seventy-seven were teenagers

1 age 12 to 19. They were from seven geographic areas.

2 [Slide.]

3 Again, th procedure was to read the carton and

4 answer questions with the carton present.

5 [Slide.]

6 The label had two notable features: "Do not use

7 if you have a weakened immune system," and "Ask the doctor

8 before use if you have a decreased ability to fight

9 infection."

10 [Slide.]

11 As with many studies, there ere problems. Again,

12 the questions about self-use were phrased "would you use the

13 product" rather than "could you use the product". This

14 possibly resulted in responses that were not entirely based

15 on the label information.

16 In this study, one purpose was to determine if

17 sexually active teenagers might misuse the product. The

18 sponsor defined "sexually active" as those teens who had had

19 sex at least once within the past 12 months. Therefore, we

20 don't know how many in the sexually active group were very

21 active sexually. In addition, some teens were not asked

22 this question at all, so they may have been misclassified.

23 It is therefore not surprising that there were no

24 differences in responses between the teens who were

25 classified as sexually active and those who were not.

1 [Slide.]

2 What did we learn from this study? Results for
3 the questions that were the same or similar to those in
4 Study 1 were similar. Scores for most of the questions were
5 in the range of 74 to 95 percent.

6 For the question about what to do after four days
7 of treatment, the score in Study 1 was 82 percent; in Study
8 2, it was 69 percent. In this study, 24 percent indicated
9 they would continue using the product beyond four days.

10 Correct scores ranged from 73 percent to 95
11 percent for use for skin rash, cold sores inside the mouth,
12 sores on the stomach, and chicken pox.

13 [Slide.]

14 With this label, however, 68 percent of the
15 immunocompromised participants incorrectly said they would
16 use the product. However, more immunocompromised patients
17 correctly answered questions about hypothetical users who
18 had their condition than questions about self-use.
19 Nevertheless, the correct response rates for the
20 hypothetical questions were still quite low.

21 [Slide.]

22 This table shows the correct response rates for
23 the four categories of immunosuppressed participants for the
24 question about their own use and use by a hypothetical
25 person with their condition. Persons on chemotherapy or

1 radiation answered correctly about their own use only 9
2 percent of the time. They answered about a hypothetical
3 person on chemotherapy or radiation treatment only 46
4 percent of the time.
5 Participants using steroids answered correctly
6 about their own use 25 percent of the time and about a
7 hypothetical person on steroids 55 percent of the time.
8 For HIV patients, the figures were 36 percent and
9 64 percent, and for those with organ transplants, the
10 figures were 64 percent and 86 percent.
11 [Slide.]
12 From the results of this study, we do not know
13 whether a label that clearly states the conditions that
14 would preclude use would be adequate for self-selection.
15 This study did not use such a label. We also do not know
16 whether sexually active teenagers would tend to misuse the
17 product for STDs.
18 [Slide.]
19 Our conclusions, therefore, are that consumers
20 understand a great deal of the label information as listed
21 here, and they also understand the information on this
22 slide.
23 [Slide.]
24 Consumers do not understand well who should not
25 use the product, whether it can be used for shingles, skin

1 rash, zoster and stomach sores, whether it can be used when
2 one has a cold, and what to do after four days.
3 [Slide.]
4 Based on Study 2, we recommend that the label
5 clearly specify the conditions that would preclude use; that
6 it indicate where on the body a cold sore occurs, clarify
7 the duration and frequency of use, and clarify the use for
8 skin rash, zoster and stomach sores.
9 [Slide.]
10 Stud 3 was qualitative research. That means it
11 was based on discussion and did not have quantifiable
12 results. It consisted of 24 interviews. All participants
13 had conditions the sponsor deemed inappropriate for using
14 the product. Twelve participants saw two different labels,
15 and 12 participants saw a third label.
16 [Slide.]
17 The results are not generalizable, however, they
18 do provide hypotheses for further testing. These
19 discussions revealed that consumers found the following
20 statements to be confusing: "Do not use if you have a
21 weakened immune system from...," and then the name of the
22 condition; "Ask a doctor if you get sick with infections
23 often."
24 They did understand "Do not use if you have HIV,
25 AIDS, cancer, or an organ transplant."

1 [Slide.]

2 the purpose of Study 4 was to focus on self-
3 selection issues among immunocompromised consumers. The
4 communications objectives were: Do consumers with
5 conditions lied on the label properly self-select use of the
6 product? and do consumers understand how long to continue
7 treatment?

8 [Slide.]

9 Again, this was one of the studies in which they
10 looked at the product label and then were asked questions
11 about it. There were 94 participants, all with a condition
12 listed on the label under the "Do not use" warning. They
13 had AIDS, HIV, cancer with chemotherapy or radiation, or
14 organ transplant. Some were in more than one category.

15 [Slide.]

16 This label specified the conditions with which the
17 product should not be used. It said: "Do not use if you
18 have HIV, AIDS, cancer, or an organ transplant."

19 [Slide.]

20 There are some major problems with this study.
21 Participants were told that the purpose of the study was to
22 determine if consumers can understand whether they can use
23 the product based on their health. They were told to take
24 their own health situation into account before answering
25 about their own use.

1 The result of these statements is to make them
2 more aware of their own health condition and its relevance
3 to the label than the typical consumer reading the label.
4 [Slide.]
5 Another problem with the study was that the
6 questions about hypothetical persons with the conditions
7 listed on the label for non-use were all to be answered the
8 same way--that the person should not use the product. This
9 type of questioning may create a response bias in which
10 responses are due in part to the prior questions rather than
11 to the actual knowledge of the participant.
12 It would have been better to include some
13 questions about conditions that did not preclude use of the
14 product.
15 [Slide.]
16 What did we learn from this study?
17 When told to consider their own health conditions,
18 80 percent responded correctly that they should not use the
19 product.
20 Responses for the hypothetical persons were
21 correct 81 percent of the time, and 78 percent knew what to
22 do if the cold sore gets worse after four days.
23 [Slide.]
24 However, we do not know whether consumers who are
25 warned on the label not to use the product will understand

1 that they should not take this product. Ordinary consumers
2 who read the label in the store will not be prompted to
3 consider their own health conditions before making a choice.
4 Although this label may have been an improvement
5 over the earlier ones that did not specify exactly which
6 persons should not use the product, we cannot tell from this
7 study if it was adequate to warn consumers who should not
8 use it.
9 [Slide.]
10 So we have several issues remaining after these
11 studies. We do not know if consumers who should not use the
12 product will understand that they should refrain from use.
13 And I would like to remind the Committees that the agency is
14 still discussing whether there are any consumers who should
15 be warned not to use the product or to consult a doctor
16 before use.
17 We do not know if sexually active teenagers may
18 misuse the product for genital sores.
19 If this product is approved for OTC use, we will
20 need to revise the labeling for the information that we have
21 identified as needing improvement.
22 Now, Dr. Linda Hu will discuss the actual use
23 study.
24 **Actual Use Study**
25 **Linda Hu, M.D.**

1 DR. HU: Good morning. I am Dr. Linda Hu from the
2 Division of Over-the-Counter Drug Products. I'll be
3 discussing the denavir actual use study which was submitted
4 to support the OTC switch application for denavir.
5 Marina Chang and Laura Lu collaborated with me in
6 the review of this study.
7 [Slide.]
8 You heard previously from Dr. Wu about the two
9 types of studies that may be performed to help determine
10 whether a product can be used safely and effectively in the
11 OTC consumer population. Dr. Lechter has just finished
12 talking to you about label comprehension studies. Now, I'll
13 be discussing the actual use study. But first, I'd like to
14 give you a little bit of background on actual use studies.
15 [Slide.]
16 Actual use studies are designed to determine how
17 the drug will be used in the OTC population without the
18 supervision of health care professionals. Typically, an
19 actual use study is designed with as few exclusion criteria
20 as possible and is considered an all-comers study. In other
21 words, anyone who wants to participate should be allowed to
22 enroll.
23 [Slide.]
24 The objectives of an actual use study depend on
25 the specific product and whether there are any product-

1 specific concerns. Examples of objectives include: how
2 well consumers can correctly self-select the product for
3 use; how well they comply with the label directions in terms
4 of dosing and duration of use; and whether the product is
5 used off-label or whether there are any populations who
6 should be targeted for non-use. Enriched subgroups may be
7 necessary to examine certain questions of interest.
8 Other objectives may be to evaluate safety or
9 efficacy in the broader OTC population.
10 Next slide, please.
11 [Slide.]
12 Specifically for denavir, the agency was
13 interested in examining the following issues: to look at
14 compliance in off-label use; to examine use by
15 immunocompromised subjects in whom the drug is not approved
16 for use and in whom systemic therapy may be preferable--
17 experience with acyclovir, which has a similar mechanisms of
18 action, indicates that resistant HSV-2 virus is found more
19 commonly in immunocompromised hosts; and lastly, whether
20 there would be inappropriate OTC use for the treatment of
21 sexually-transmitted diseases, which could result in a delay
22 in diagnosis and treatment.
23 Next slide.
24 [Slide.]
25 The study objectives as stated by the sponsor are

1 listed in this slide. They are: to determine the use
2 patterns in a simulated OTC setting with self-selected cold
3 sore suffers; to look at the rate at which participants with
4 risk factors inappropriately chose to use the drug; to look
5 at safety in OTC use; and perceived overall effectiveness.
6 [Slide.]
7 The denavir actual use study was a multicenter,
8 open label, all-comers actual use trial in those age 12
9 years and above. It was conducted to provide information
10 about the use and safety of the drug in a setting that
11 mimicked the circumstances of OTC use. A total of 8,854
12 subjects who were troubled by cold sores were recruited from
13 14 metropolitan areas using newspaper and television
14 advertising, random, digit-dialed calls to people in ZIP
15 Code areas near the enrollment sites, and in-store
16 advertisements.
17 Subjects were enrolled in 86 pharmacies and
18 interviewed by telephone to assess drug use and outcome.
19 Recruited subjects were screened to determine if they chose
20 to participate and use the study drug, and if so, they were
21 dispensed one tube of study medication.
22 Eight thousand five hundred and thirty-four
23 subjects chose to enroll.
24 Next slide.
25 [Slide.]

1 Study data were collected from enrolled subjects
2 principally by the use of telephone interviews. These were
3 computer-assisted, scripted interviews to obtain information
4 on the following. They were to look at treatment decisions,
5 such as the indication for use, the location of the cold
6 sore; to look at the use of the drug including the number of
7 applications and duration of study, and number of days used;
8 to look at medical status with a particular focus on immune
9 history; and to look at usage outcomes, primarily in the way
10 of adverse events.
11 Next slide.
12 [Slide.]
13 The recruitment sties included areas with
14 relatively high proportions of immunocompromised subjects.
15 However, there was no targeted recruitment of a sexually
16 active or STD subgroup.
17 The sponsor divided enrollees into a respondent
18 and non-respondent group. Respondents were those enrollees
19 who used the drug and completed a normal follow-up telephone
20 interview during the study period. Non-respondents were
21 those individuals who did not complete a normal telephone
22 interview.
23 [Slide.]
24 Of the 8,534 subjects who chose to enroll and use
25 the study drug, 4,751 subjects were respondents. This

1 comprised 56 percent of enrollees. Three thousand seven
2 hundred eighty-three subjects, or about 44 percent of
3 enrollees, were non-respondents. Therefore, you need to
4 keep in mind when looking at the study results that there is
5 a large number of enrollees in whom we have no usage or
6 history data.
7 Medical history with regard to immune status was
8 not able to be obtained in about 35 percent of the
9 enrollees, or 3,020 subjects.
10 Out of the non-respondents, there were 2,142, or
11 25 percent of enrollees, who had not used the study
12 medication prior to the end of the study period; another
13 1,193, or 14 percent, were lost to follow-up.
14 Of those recruited, 323 did not participate in the
15 study and did not receive study drug. These consumers
16 either eliminate themselves after reading the label or were
17 disqualified because they did not have a home or work
18 telephone.
19 [Slide.]
20 Study results. A high fraction, or about 96
21 percent of respondents, appropriately chose to use the study
22 drug. Reasons contributing to this high response rate may
23 have been that the study population was predominantly well-
24 educated, with 73 percent having some college education or
25 beyond, including 38 percent having either a college degree

1 or postgraduate education. This group was more highly
2 educated than the general U.S. population.
3 The recruitment materials provided coaching to
4 subjects that would not normally be available in the OTC
5 marketplace. This may have decreased an appropriate use of
6 the study drug among study participants.
7 Interested consumers were given an enrollment
8 package and were asked to fill out some information about
9 their cold sore history and some demographics. Next, they
10 were directed to read a carton label and then to proceed on
11 to a decision form.
12 [Slide.]
13 The decision form is shown overhead. Basically,
14 participants were asked: Do you think this medicine is
15 right for you? and if not, to please indicate the reason.
16 The decision form explicitly lists several reasons
17 why participants should not participate--for instance, I am
18 pregnant; I have problems with my immune system, et cetera.
19 Presenting the list of reason why not to use
20 denavir on the decision form could have alerted potential
21 participants that the drug was not appropriate for them to
22 use and could have influenced the study results.
23 [Slide.]
24 In general, the medicine was used less frequently
25 than would have been expected given the label directions.

1 While the label directions state to "Apply the drug every
2 two hours while awake," the number of applications per day
3 in general was less frequent than that seen in the clinical
4 trials. The mean was 4.6 times per day in the actual use
5 trial versus 7.7 to 8.4 times per day in the clinical
6 trials.
7 [Slide.]
8 The rate of inappropriate use by immunocompromised
9 consumers cannot be accurately determined, since medical
10 history data was not obtained in all those who did not use
11 the study medication. Immune status could not be determined
12 for 35 percent of enrollees, or 3,020 subjects.
13 However, out of the 4,751 respondents who did use
14 the drug and did have an interview, 135 subjects were
15 evaluated by the sponsor as being immunocompromised to some
16 degree.
17 Of the 135 subjects identified as
18 immunocompromised by the sponsor, 15, or 11 percent of
19 those, spoke to a doctor about the study drug, and this
20 could be consistent with the label directions for use.
21 Another 23 subjects chose not to enroll or participate in
22 the study because of, quote-unquote "immune system
23 problems."
24 [Slide.]
25 No sexually active or STD cohort was recruited,

1 and no STD history was obtained. Of 66 respondents who used
2 the medicine on cold sores located on the body other than
3 the face, there were eight possible genital herpes.
4 [Slide.]
5 There were 13 pregnant and 20 nursing women of
6 3,021 female respondents, with an additional 2,076 female
7 subjects whose pregnancy and nursing status was unknown.
8 [Slide.]
9 There were 35 enrollees who stated that they used
10 the drug for something other than a cold sore, and of 66 who
11 responded that the cold sore was located on a part of the
12 body other than the face, eight of these were mentioned
13 previously as having lesions that could be consistent with
14 genital herpes. Another 11 people used the drug in
15 locations such as the hand, calf and back. One subject used
16 the medication for chicken pox.
17 [Slide.]
18 There was also use by non-enrolled users--that is,
19 by persons other than the person who enrolled in the study.
20 There were 176 secondary users of the drug, of whom 122 were
21 lost to follow-up. The study did interview 54 of these
22 respondents and showed that 39 percent of the secondary
23 users who were interviewed did not read the label. Eight
24 secondary users were children under the age of 12.
25 [Slide.]

1 The telephone interview included questions which
2 screened for adverse events--questions asking whether
3 participants experienced discomfort or targeted events which
4 could be considered serious by the FDA regulatory definition
5 were asked of respondents. For example, these questions
6 were: Since you enrolled, have you been admitted to a
7 hospital as an inpatient? Have you had any health events
8 which you considered life-threatening?
9 No serious adverse events related to the use of
10 the study drug were reported by the sponsor. The use of
11 denavir was generally well-tolerated, with reported adverse
12 events being generally minor.
13 The adverse event rates evaluate as possibly or
14 probably related to use of the drug were reported by about 6
15 percent of respondents, and the most recently reported
16 events were application site reaction, headache, reaction
17 aggravation and pain.
18 There were also several other cases of allergic
19 reactions, including asthma, hives, rashes, and several
20 application site reactions that may have also been allergic
21 in nature. A label warning may be necessary alerting
22 consumers that they may experience transient burning,
23 stinging or pain with use of the product and directing them
24 to discontinue use if allergy symptoms develop.
25 [Slide.]

1 The label is the same one that was tested in label
2 comprehension Study 2, which had problems communicating the
3 immunocompromised concept.
4 [Slide.]
5 In conclusion, although a high proportion of
6 respondents correctly chose to use the drug under the study
7 conditions, there are a number of caveats that are worth
8 noting. There was no usage or Hx information obtained on
9 many enrollees, enrollees were highly educated, and there
10 was some coaching done during the recruitment process. The
11 medication was used less frequently than indicated on the
12 label--4.6 applications per day versus about 7.7 in the
13 clinical trials.
14 This actual use study does not assure us that
15 consumers or immunocompromised consumers will not use the
16 study drug or that they will ask a doctor prior to use. In
17 addition, this study does not determine whether
18 inappropriate use to treat STDs will be a problem in OTC
19 use.
20 Thank you for your attention. Now I'll turn the
21 presentation back to Dr. Teresa Wu.
22 **Safety: OTC**
23 **Teresa Wu, M.D., Ph.D.**
24 [Slide.]
25 DR. WU: Next, we shall comment on the company's

1 OTC safety data. I shall first review the applicant's post-
2 marketing spontaneous reports of adverse events, and then
3 comment on applicant's resistance data and on their proposed
4 viral resistance surveillance program, and finally, I will
5 summarize FDA's overall assessment with respect to benefits
6 versus risks.
7 Next slide, please.
8 [Slide.]
9 After the approval of penciclovir, the safety
10 information has been continually collected by applicant
11 through a spontaneous reporting system. Such report has
12 indicated that the adverse events are of very low incidence.
13 But a caution about the spontaneous report is that such a
14 passive surveillance system is subject to limitations such
15 as under-reporting, reporting bias and suboptimal data
16 quality.
17 In addition to post-marketing spontaneous
18 reporting, the company conducted two surveillance studies.
19 These surveillance studies were based on two UK computerized
20 medical record reporting systems. One is the General
21 Practice Research Database, abbreviated as GPRD; the second
22 one is MediPlus.
23 Although these two surveillance studies did not
24 identify adverse events differently from that reported in
25 clinical trials, the sample size of between 400 to 700 per

1 treatment group is felt to be too small to detect rare or
2 previously unrecognized events.
3 In a post-marketing situation where the drug
4 product is administered to a greater number of subjects,
5 rare side effects may occur in a sub-population which was
6 not significantly represented in clinical trials.
7 Despite the small sample size of these two
8 surveillance studies, there was a finding of around 19
9 percent off-label use of denavir was reported even when
10 denavir was used as a prescription drug. However, the
11 information on the nature of the off-label use was
12 incomplete, but we did find that genital herpes and herpes
13 zoster were among those.
14 Next slide, please.
15 [Slide.]
16 Next, we would like to comment on the company's
17 penciclovir resistance data based on the paired isolates
18 from these two pivotal clinical trials.
19 The company concludes that "Analysis of paired HSV
20 isolates from patients with recurrent herpes labialis shows
21 that the use of topical penciclovir cream is not associated
22 with the development of resistance virus."
23 Next slide, please.
24 [Slide.]
25 We have three comments regarding this applicant's

1 conclusions. The trend analysis was based on a very short
2 duration of drug exposure in a single episode of the herpes
3 infection. The duration of treatment was between one to
4 three days.
5 Secondly, while the investigator of Study 024--
6 this is the U.S. Study--generally followed the virological
7 procedures specified in the protocol, investigators of Study
8 025, the international study, were less adherent to pre-
9 specified procedures.
10 Thirdly, most isolates were tested for
11 susceptibility to penciclovir by either virology laboratory
12 identified here as "A" and "B". As can be seen from this
13 slide, both labs have very different IC-50--about a 10-fold
14 difference--for an HSV-1 penciclovir-sensitive control.
15 Such discrepancy may suggest in these two laboratories
16 either a different control strain was used, or a different
17 susceptibility procedure was used, or this is an inherent
18 inter-laboratory variation, or all the above.
19 I should point out that the technique used by both
20 laboratories was plaque reduction assay.
21 [Slide.]
22 Next, I would like comment on the company's
23 prevalence data for penciclovir resistance. This data was
24 based on IV penciclovir study and famciclovir studies. The
25 company concludes: "The prevalence of penciclovir-resistant

1 HSV isolates from patients in the topical penciclovir trials
2 is very similar to that for oral famciclovir in
3 immunocompetent patients."
4 The company also concludes: "The incidence of
5 resistant HSV is equally low in both immunocompetent and
6 immunocompromised populations."
7 The conclusions were based on data-pooling from
8 six clinical trials.
9 [Slide.]
10 The results were based on pooling data from nine
11 clinical trials in which four different virology
12 laboratories performed susceptibility testing. There were
13 three different assay methods used--plaque reduction assay,
14 ELISA assay, and DNA hybridization reduction assay. Since
15 the comparability of the results from these three methods is
16 unclear, and the definition of resistant IC-50 values for
17 each assay were not defined, ew find that pooling data based
18 on different assay procedures makes the results difficult to
19 interpret.
20 Secondly, the database for immunocompromised
21 patients was relatively small, consisting of 245 patients.
22 Of these 245 patients, 72 were HIV-infected. Among this
23 HIV-infected patient population, only 14 had an entry CD-4
24 number less than 200. Therefore, the report of a low
25 incidence rate of viral resistance was based on a population

1 including only a very small number of advanced HIV subjects.

2 Next slide.

3 [Slide.]

4 Next, I would like to comment on the company's

5 acyclovir-resistant HSV data. These data were based on two

6 surveys published. The company's conclusion is that: "Data

7 from two surveys in the U.S. and in the UK published in 1998

8 confirm that the prevalence of acyclovir-resistant HSV is

9 stable since acyclovir was approved in the early 1980s."

10 However, we feel that the impact of OTC use on the

11 prevalence of acyclovir-resistant HSV cannot be determined

12 based on these two reports because the study done in the

13 U.S.--a country where, at the time, no OTC use of topical

14 acyclovir was approved--and the one done in the UK was

15 conducted prior to OTC approval.

16 Next slide.

17 [Slide.]

18 Next, I would like to comment on the company's

19 proposed surveillance study. This slide simply reviews the

20 company's proposal. As presented in applicant's outline for

21 the proposed viral resistance surveillance program, four

22 studies are planned after topical penciclovir approval--a

23 survey in the U.S., in the UK, a repeat use study, and a

24 survey in HIV-infected individuals.

25 It appears that the design of these four studies

1 is focused on the targeted number of isolates or patients
2 without giving consideration to other aspects of a program
3 from an epidemiological perspective.
4 [Slide.]
5 Specifically, several issues, as listed in this
6 slide and subsequent ones, have not been addressed in the
7 proposed study design. First, to ensure data comparability,
8 the procedure for the performance of the susceptibility
9 testing should be standardized among labs, and a proper
10 quality assurance program should be an integral part of the
11 surveillance program.
12 Second, the collection of isolates should have a
13 broad representation with respect to age, race, gender,
14 disease status and the pattern of use and locality.
15 Next slide, please.
16 [Slide.]
17 The surveillance program should be of a long-term
18 commitment with the goal of surveillance of emergence of
19 viral resistance over time. Consequently, the program
20 should include a provision for delivering timely information
21 on a regular basis.
22 Lastly, research is needed for establishing
23 threshold levels of resistance that could be used as signals
24 or alerting actions in the course of surveillance.
25 Next slide, please.

1 [Slide.]

2 My last slide will summarize our overall
3 assessment based on benefit and risk ratio of OTC denavir.
4 Based on the clinical trial, denavir has shown modest
5 clinical benefit. It has low frequency of adverse events
6 based on clinical trials as well as post-marketing
7 surveillance. The viral resistance data as presented by the
8 company is limited. The label comprehension study shows the
9 difficulty in one group that is the subject of low literacy
10 background, and the definition of immunocompromised also
11 presents difficulties.

12 Because of the study design, we do not know what
13 is the potential for misuse among individuals having an STD
14 or inappropriate self-selection by immunocompromised
15 patients.

16 This concludes FDA's assessment. Thank you.

17 DR. BRASS: Thank you.

18 Are there questions for any of the FDA presenters
19 from the panel?

20 Dr. Woolson?

21 **Questions from Advisory Committees**

22 DR. WOOLSON: Yes. One of your conclusions here
23 is the modest clinical benefits, and I'll take this as an
24 opportunity to raise the general question I have had about
25 these studies.

1 It seems that there have been a lot of people
2 randomized who are not included in the various analyses, and
3 in particular for the assessment of the clinical effects,
4 the intention to treat populations that the FDA used when
5 they were originally assessing Studies 024 and 025 differ
6 from the intention to treat that the sponsor had.
7 Today you mentioned that there was another issue
8 regarding how loss to follow-up was handled in the analysis.
9 I wondered if you could in a nutshell just tell us how the
10 clinical effects are dependent on the definitions that are
11 actually being used for patient definitions, for inclusion,
12 or on how the loss to follow-up issue was dealt with.
13 DR. WU: First, let me define what is "intent to
14 treat" patient population. This was defined as anyone who
15 had the disease of interest irrespective of whether they
16 received treatment or not. This is the definition of
17 "intent to treat." Therefore, even though there were about
18 2,000 patients being randomized, only 1,500 patients
19 qualified under this definition of intent to treat. This is
20 number one.
21 Number two, the extent of patients missing follow-
22 up information was quite high for both studies--in the
23 neighborhood of 22 percent. Reasons for loss to follow-up
24 were missing data, including they had the infection but did
25 not choose to receive the drug--you will recall this is a

1 patient-initiated study design; some never return to the
2 clinic, so the extent of the loss to follow-up is very high.
3 Thirdly, you wanted me to comment on the
4 difference in methodology between FDA and the company. I
5 can simply describe that the company uses an assumption
6 approach, that is, those without follow-up data are
7 arbitrarily given a duration of lesion based on several
8 quartiles of those patients who did have that information,
9 whether this is the first quartile, whether this is the
10 middle quartile, or whether it is the third quartile. So
11 this is their assumption approach.
12 As far as FDA, FDA used a more conservative
13 approach since their duration is unknown, so for those who
14 did not have follow-up information, the treatment effect
15 between the two groups was assigned as zero. So this
16 slightly different methodology resulted in a slightly
17 different magnitude of treatment effect, but overall, the
18 difference is considered to be very small.
19 DR. WOOLSON: As a follow-up to that, could you
20 just comment on the issue of the clinical effect versus the
21 significance that we are seeing in the data? I am a
22 statistician, and a half-day doesn't seem like a whole lot
23 to me for this, and I guess I was wondering if you could
24 give me FDA's perspective on this as well, whether you think
25 this is an important difference.

1 DR. WU: This disease is a self-limited disease,
2 so to expect a huge effect is rather unlikely, and the
3 disease duration, the natural course of it, is short. So we
4 feel that one-half day is clinically significant. We also
5 agree that the magnitude of the reduction is of a modest
6 degree.
7 DR. BRASS: Yes, Dr. Masur?
8 DR. MASUR: Could you review--if this drug were
9 approved for over-the-counter use, and resistance or misuse
10 did turn out to be a problem one, five, or ten years hence,
11 what is the statutory ability of the agency and the
12 precedent for withdrawing OTC approval?
13 DR. KATZ: Could you repeat the question, please?
14 DR. MASUR: If the drug were shown to have some
15 problem in terms of resistance or misuse after it were
16 approved, is there some precedent for withdrawing approval,
17 and is there statutory ability to withdraw approval for OTC
18 use once granted?
19 DR. KATZ; Yes, there is. It is basically the
20 same as what would happen with--let's say it were a
21 prescription drug, and one found out there were some serious
22 adverse events that were seen. A product can be withdrawn,
23 and it can abe done the same way in the OTC world, too. If
24 the product is found either to have adverse events that have
25 not been determined prior to the time of approval, or if

1 something else arises after approval that the product should
2 not be available OTC, the approval can be withdrawn.
3 DR. BRASS: Are there any other questions or
4 issues for the agency to address?
5 [No response.]
6 DR. BRASS: If I could just ask one, then. You
7 indicated that you have reached no decision about whether or
8 not you are concerned about preventing OTC use by
9 immunocompromised patients. Could you share with us your
10 current thinking as to what the concern would be in not
11 warning them not to use it--I don't know how many negatives
12 I can get into one sentence there. What is your concern if
13 immunocompromised patients do use the product?
14 DR. WU: Our concern stems from--immunocompromised
15 subjects should understand the label and therefore know they
16 should consult their doctor first.
17 DR. BRASS: No, that wasn't my question. My
18 question is why should they. What is the danger or what is
19 the safety concern if immunocompromised patients do use this
20 product for cold sores over-the-counter?
21 DR. WU: The reason is in case they did not
22 respond clinically very well, and those are the subjects who
23 should receive the other type of treatment for their
24 infections because of the risk of resistance issues in this
25 type of patient population.

1 DR. BRASS: So, is it that you are informing them
2 that they may not have benefits, or are you suggesting that
3 there is an increased risk of resistance developing if they
4 do use it?
5 DR. WU: There is the potential of not being able
6 to recognize resistance in this type of patient population.
7 DR. BRASS: And is that based on a concern, or is
8 that based on data?
9 DR. WU: This is based on concern.
10 DR. BRASS: Okay.
11 Please, Dr. Lipsky.
12 DR. LIPSKY: Maybe I am making some decimal errors
13 in the numbers, but going over what the sponsor submitted in
14 their book on potential use and how much of this tonnage is
15 going to be out there compared to what currently is used,
16 does the FDA have numbers on that?
17 DR. WU: We do not have those numbers.
18 DR. LIPSKY: Then, I am curious, because on page
19 102 of the handbook which the sponsor supplied us, they
20 state: "With respect to the potential of penciclovir use in
21 the United States, if all 40 million people estimated to
22 have recurrent herpes labialis were to use a 1.5 gram tube
23 per year, this would result in 600 kilograms of penciclovir
24 use annually."
25 I do that calculation, and I get more like 60,000

1 kilograms--

2 DR. BRASS: Maybe the difference is product versus

3 weight of--how much penciclovir versus how much gross

4 product.

5 DR. LIPSKY: Oh, I see.

6 DR. BRASS: It's not 1.5 grams of penciclovir.

7 Dr. LIPSKY: Because it's a very small--

8 DR. BRASS: Is that correct, sponsor?

9 DR. MARKS: Yes.

10 DR. BRASS: That's the difference.

11 DR. LIPSKY: So the actual penciclovir in the

12 ointment is actually a thousandth of the formulation?

13 DR. MARKS: It is one percent penciclovir cream.

14 DR. LIPSKY: So, one one-hundredth. It still

15 would be off by an order of magnitude. It would be useful

16 to have some sort of feel for exactly what is the intensity

17 of this antiviral compared to what is out there, so we can

18 put that into the equation on what impact it could have on

19 resistance, and maybe if either the sponsor or the FDA or

20 someone could come up to reconfirm the numbers which they

21 state, it would be useful.

22 DR. BRASS: Perhaps this can come up during this

23 afternoon's discussion, and in the interim, the sponsor can

24 try to synthesize some data on that for us.

25 Yes?

1 DR. EL-SADR: I don't know if the FDA has any
2 information on this issue, but I was curious when they were
3 presenting the data on the comprehension of the label and so
4 on--if you did the same thing with your package inserts for
5 physicians, I am really curious as to how many would misuse
6 a product and how many would identify the entity and so on.
7 It is sort of an alarming issue that I hadn't thought about
8 until sitting on this committee made me think about it,
9 actually.
10 DR. YOGEV: You have the answer. The answer is 17
11 to 19 percent were off-label.
12 DR. EL-SADR: That's off-label, but that's
13 different. I think off-label is one issue. Off-label is
14 using it for another purpose.
15 DR. YOGEV: That's off-label--
16 DR. EL-SADR: I mean, for example, giving the
17 wrong dosage, the wrong duration, et cetera. Do you have
18 any comparative data, or do you try to get this information
19 for package inserts?
20 DR. LECHTER: I am not aware of any studies that
21 have been done on physician labeling. However, it may make
22 you happy to learn that ew are working on revising physician
23 labeling for prescription products.
24 DR. BRASS: If there are no additional questions,
25 we'll adjourn at this time for lunch, and we will reconvene

1 promptly at one o'clock.

2 Thank you.

3 [Whereupon, at 12:05 p.m., the proceedings were

4 recessed, to reconvene at 1:00 p.m. this same day.]

1 AFTERNOON SESSION

2 [1:00 p.m.]

3 DR. BRASS: We are going to begin the afternoon

4 session with the open public hearing. Four individuals have

5 requested time to speak, and two additional individuals have

6 submitted written commentary which will be read into the

7 proceedings.

8 As each of the people who are present comes up to

9 address the proceedings, if you would please be sure not

10 only to identify yourself and your affiliation, but please

11 identify who, if anybody, is sponsoring your visit with us

12 today and any conflict of interest which is appropriate for

13 the panel to be aware of.

14 The first individual requesting time is Dr. Earl

15 Kern, from the University of Alabama, Birmingham.

16 **Open Public Hearing**

17 DR. KERN: I am Earl Kern, and I have cold sores.

18 I would like to thank the Committees and the

19 agencies for giving us an opportunity to tell you a little

20 bit about some of the activities that we have had ongoing

21 for the last couple of years in the area of antiviral

22 resistance.

23 DR. BRASS: I'm sorry. Is anybody sponsoring your

24 visit here today?

25 DR. KERN: Well, I'm going to get to that, okay?

1 Can we handle that as we go?

2 Can I have the first slide?

3 [Slide.]

4 DR. KERN: As was pointed out this morning at the
5 January 1995 Committee on OTC Switch for Zovirax, there was
6 significant concern about the development of resistance
7 through the use of OTC acyclovir. In response to this, then
8 Burroughs Wellcome Company funded a task force to actually
9 study the problem of herpes simple virus resistance to
10 acyclovir.

11 As part of this, the Task Force on HSV Resistance
12 was formed. It operates as an ad hoc committee under the
13 International Society for Antiviral Research, and the Task
14 Force activities are currently sponsored by Glaxo Wellcome,
15 Incorporated and by SmithKline Beecham.

16 [Slide.]

17 I was asked to chair and organize this Task Force,
18 and as such as the chair and also as part of my other
19 activities with regard to resistance, I have in fact
20 received reimbursements and honoraria from both Glaxo
21 Wellcome and SmithKline Beecham. However, according to the
22 guidelines for my own institution, these would not be
23 considered to be significant.

24 The committee as currently constituted is listed
25 here. In addition to myself, it includes Larry Corey with

1 the University of Washington; Clyde Crumpacker from Harvard;
2 Graham Darby, Glaxo Wellcome; Phil Pellett, CDC; Steve
3 Sacks, University of British Columbia; and Steve Straus from
4 NIH.
5 We think we have an accomplished group of
6 investigators. They are all scientists who have done a lot
7 of work in the area of resistance. They represent
8 academics, NIH as well as CDC.
9 Next slide, please.
10 [Slide.]
11 DR. KERN: The purpose of this Task Force
12 originally was to first function as an independent group,
13 although we are in fact supported by industry, moneys
14 currently come in to the International Society for Antiviral
15 Research which are then disbursed out through the Task
16 Force. So we feel that we can in fact act autonomously and
17 independently from the companies that are supporting the
18 work.
19 Among of our purposes are to review existing data
20 on ACV resistance and now, certainly, PCV resistance; to
21 define both laboratory resistance and clinical resistance;
22 to identify and prioritize scientifically relevant issues
23 regarding increased use of antiviral drugs; to sponsor or
24 conduct surveillance studies to monitor resistance; to
25 suggest studies to be carried out by sponsors of similar

1 antiviral drugs that may come to the market; and to review
2 new data on resistance and provide recommendations to the
3 community.
4 One of the problems we have with the last items is
5 whom do we make these recommendations to. I think there are
6 ongoing discussions to expand the role of the Task Force
7 into some kind of working group involving the CDC, FDA, NIH,
8 and other agencies so we really do have a watch group, if
9 you will, and once we get numbers that look like they may be
10 a problem, we have someone who can immediately speak to
11 these. And over the next few months, we'll try to put some
12 kind of working group in place to cover that.
13 [Slide.]
14 First, I'd like to describe to you two
15 surveillance studies that were completed between October
16 1996 and April 1998. These are studies that were
17 commissioned by the Task Force and were contracted to CDC,
18 and CDC ran the two studies. Michelle Reyes was the PI on
19 both studies.
20 Study Number 1 is in the immunocompetent host in
21 STD clinics. Just to quickly summarize, we had 1,834
22 patients who had a positive HSV culture. Six of these were
23 resistant to acyclovir, for a frequency of 0.3 percent--
24 which is virtually identical to all the historical data that
25 was presented this morning.

1 The second study was done in HIV patients, again
2 conducted by the same group of people, the Task Force, CDC
3 and Glaxo Wellcome. In this case, we had 238 patients with
4 a positive culture, 13 of whom were resistant to acyclovir,
5 with a frequency of 5.4 percent--again, identical to the
6 data that were presented historically.
7 [Slide.]
8 Of these 19 resistant isolates--these have all
9 been confirmed by two independent laboratories--they were
10 100 percent HSV-2; 84 percent of them were males; 84 percent
11 used acyclovir, not PCV--acyclovir, valacylovir, or
12 famcylovir; 16 of 19 had previously used the drug; 16
13 percent, or 3, had never used acyclovir; 7 had used topical
14 acyclovir, and 9 had use parenteral drug.
15 [Slide.]
16 Now, a study that is ongoing. The CDC elected to
17 not continue doing surveillance studies in April. The Task
18 Force felt that the immunocompromised host is a great
19 sentinel population because resistant virus is actually
20 manifest and enhanced in this population. So the Task Force
21 elected to conduct their own surveillance studies, and this
22 has been done. These are multi-institutional studies. John
23 Gnann is the principal investigator. This is a continuation
24 of Study Number 2 which I showed you previously.
25 This study began in April 1998 and is current to

1 October 1998 and is continuing. So far, we have collected
2 168 cultures, 70 of which were positive for virus; 56 were
3 HSV-2; 14 were HSV-1.
4 This study differed from the previous two in that
5 we broadened our entrance criteria in this study to take
6 oral lesions as well as genital lesions, because as you
7 know, we feel that there is data lacking on HSV-1, so we
8 hope to increase our database with HSV-1. And clearly,
9 having gotten 14 isolates, we are starting to do that.
10 Of that 70, 61 have been tested for resistance,
11 and 6 of these are resistant to ACV and/or PCV. The
12 frequency, then, is 9.8 percent, which may seem a little
13 high, but let me remind you the numbers are still very
14 small. At 61, I would not make anything of the increased
15 frequency at this point. If we get to 500 samples, and the
16 frequency is higher, then I think we would start to get a
17 little bit concerned.
18 So the goal of the Task Force is to continue to
19 collect about 500 HSV-positive patients or other
20 immunosuppressed patients per year for five years. We feel
21 that we have a commitment to industry to do this. We feel
22 that five years is an absolute minimum. At that point in
23 time--in fact, even ongoing--the data should be continually
24 analyzed, periodically looked at and evaluated by the Task
25 Force and related people.

1 [Slide.]

2 DR. KERN: Other studies that are ongoing--through
3 the Task Force, a mathematical model was developed similar
4 to the one you heard about this morning to determine if
5 treatment rates were increased, what would be the key
6 factors in determining increased resistance. That paper was
7 published in Nature Medicine earlier this year by Sally
8 Blower et al., and a quick summary of that basically tells
9 you that under the worst case scenario, that is, doubling
10 the amount of drug, frequent sexual episodes, numerous
11 partners, you come out with something like 50 to 100 years
12 in order to get a significant increase in frequency.

13 There has been concern about low dose, and it was
14 mentioned a couple of times this morning--does low dose
15 predict or predicate the development of resistance? We have
16 had a study ongoing in immunocompetent patients looking at
17 low-dose acyclovir, with Steve Sacks being the principal
18 investigator. That study was just recently completed, and
19 the data are currently being analyzed.

20 Another ongoing study is looking at the
21 development of resistance to ACV in bone marrow transplant
22 patients who have a high incidence of HSV-1. This is a
23 study in Seattle under the direction of Anna Wald.

24 [Slide.]

25 DR. KERN: For laboratory studies, the Task Force

1 has taken the approach that the characterization of these
2 isolates is extremely important. We really feel that we are
3 going to learn more about resistance through the
4 characterization of the isolates than we will from just
5 frequency data. So intense laboratory studies are ongoing
6 in a number of laboratories, including Glaxo Wellcome,
7 SmithKline Beecham, my own laboratory, and others.
8 All the sensitivity testing for all of these
9 studies was done in a central laboratory with complete
10 protocols,, quality assurances on board, positive and
11 negative controls. All isolates that were deemed to be
12 resistant were confirmed in two additional laboratories.
13 Cross-susceptibility of all acyclovir or PCV-resistant
14 mutants have been done to gancyclovir, foscarnat [ph.] and
15 cydofamvir. Intense studies looking at the phenotypic,
16 genotypic and biochemical analysis of the TK genes--that is,
17 we have sequenced the thymidine kinase gene in all 19 of
18 these, and there is most interesting data coming out of
19 this.
20 In addition to that, virulence and latency in
21 animal model studies are ongoing to determine what these
22 mutants that are supposedly avirulent, the TK-deficient
23 mutants, how these really behave.
24 So there is a large collection of information that
25 is going to come out of these studies from the laboratory

1 that will be unprecedented in studies that have been done in
2 the past. Remember--these are not laboratory-resistant
3 mutants; these are all naturally-occurring mutants out of
4 clinical studies.
5 [Slide.]
6 DR. KERN: So from the Task Force studies, we
7 believe that acyclovir-resistant herpes simplex infections
8 do not appear to be a problem at the present time. The
9 incidence of these infections has not increased since the
10 introduction of acyclovir and penciclovir. However, the
11 rapid identification of a problem in the future will depend
12 on continued surveillance programs similar to those carried
13 out by the Task Force and CDC.
14 Thank you.
15 DR. BRASS: Thank you.
16 Perhaps you could just briefly comment on how you
17 would suggest the panel extrapolate that available data to
18 HSV-1, the issue of resistance in the immunocompetent host,
19 and the concern about the use of a topical product over-the-
20 counter by immunocompromised patients.
21 DR. KERN: You are going to get my personal
22 opinion here, not necessarily the Task Force opinion.
23 DR. BRASS: I understand.
24 DR. KERN: We have yet to get a resistant HSV-1.
25 They appear to be extremely rare. And I think Dr. Levin

1 gave you a number of reasons this morning why that is true.

2 The immunocompetent host, again as Dr. Levin very

3 nicely diagramed, clears these virus infections very well

4 because they are self-limiting infections. The host

5 response does a very nice job of clearing both sensitive

6 virus as well as resistant virus.

7 So that in my own opinion, to go out and spend

8 millions of dollars and collect thousands and thousands and

9 thousands of isolates from immunocompetent patients is not

10 the best use of one's dollars. I clearly prefer to put our

11 money in the immunocompromised, where I think even if you

12 got mixed populations, in the immunocompromised host, the

13 TK-positives in those mixed combinations are amplified. So,

14 in the immunocompromised host, we stand a much better chance

15 of isolating resistant virus than we do in the

16 immunocompetent. And these studies have all been done in

17 animals as well. You can actually select out a TK variant

18 out of a mixed population by just putting the thing into a

19 mouse.

20 So I guess my opinion, and I think the Task Force

21 opinion, is that doing ongoing surveillance studies in the

22 immunocompromised host gives one the best chance of picking

23 up resistance virus. From that point, then, I think one

24 needs to periodically go out and look at the immunocompetent

25 host as well.

1 The other issue that has been raised is should we
2 be looking at children, and we think that that is an
3 excellent idea. One problem we have as a Task Force is that
4 we have all these great ideas, but we don't have a lot of
5 money to pay for them, so it's kind of whatever we can do
6 with what we can get.
7 DR. BRASS: Are there any other brief questions
8 for Dr. Kern?
9 Yes, Dr. Yogev?
10 DR. YOGEV: I understand only a small number, only
11 six, were resistant in the survey. How many of those were
12 HSV-1?
13 DR. KERN: None. We still do not have a resistant
14 HSV-1 isolate. I'm dying to get one. I mean, we can make
15 it in vitro; we know it happens, because they are easy to
16 make in vitro. But we have yet to get one out of two and a
17 half years of clinical surveillance studies.
18 DR. BRASS: Yes, please.
19 DR. EL-SADR: From the presentation this morning,
20 I thought the Task Force was embarking on a study in the
21 United States on oral isolates of herpes.
22 DR. KERN: I'm sorry?
23 DR. BRASS: That's not them; that's the company.
24 DR. EL-SADR: I see. I thought it was in
25 collaboration with the Task Force. No?

1 DR. KERN: The only thing that I've done, as I
2 mentioned, is we have broadened our entrance criteria on our
3 current immunocompromised studies to include oral lesions.
4 In fact, if a patient has a genital and an oral lesion
5 concomitantly, we will sample both. We really are looking
6 to find HSV-1 isolates, so we are broadening our criteria
7 from the original genital HSV-2 studies to include HSV-1.
8 DR. BRASS: Thank you very much, Dr. Kern.
9 Our next speaker is Dr. Richard Whitley, also from
10 the University of Alabama, Birmingham.
11 DR. WHITLEY: I am here as a spokesperson for
12 seven independent academic physicians who were asked by
13 SmithKline Beecham to review the topical proposal. I
14 neither have grant support nor a current consulting
15 agreement with SmithKline Beecham, although I probably have
16 consulted and received honoraria from every pharmaceutical
17 firm in the world, so I am so conflicted I guess I can't be
18 any more conflicted.
19 I think it is important to document the people who
20 participated in this review and what the purpose was. The
21 panel consisted of Merle Sandy, Professor of Medicine and
22 Chairman of the Department of Medicine at the University of
23 Utah; Larry Drew, Professor of Medicine at Mount Zion
24 Hospital in San Francisco as well as University of
25 California San Francisco and the Stanford Healthcare System;

1 Fred Hayden, Professor of Medicine at the University of
2 Virginia; Larry Corey, Professor of Medicine at the
3 University of Washington in Seattle; Earl Kern, my colleague
4 at the University of Alabama at Birmingham; Bob Moellering,
5 Chairman of Medicine at Beth Israel Deaconess Hospital in
6 Boston, and myself.
7 We were asked to review by SmithKline Beecham as
8 an independent panel the data that have been presented to
9 you today. The process which we undertook was to listen to
10 formal presentations both for and against the over-the-
11 counter licensure of denavir and then meet in private, with
12 no company representative present, to discuss and draft a
13 report.
14 The report that we have drafted has been
15 circulated to Committee members. It is a report that will
16 be submitted in expanded form to Clinical Infectious
17 Diseases for publication. I want to emphasize that there
18 was no company participation in the generation of the report
19 at all.
20 It is important to document some of the events
21 that have transpired. Of the seven members of the panel,
22 four were members of a panel that similarly reviewed
23 acyclovir over-the-counter back in 1995-1996 and did have
24 that experienced, and it was that group that weighed against
25 over-the-counter licensure of the systemic formulation of

1 acyclovir for genital herpes.

2 The data that ere looked at included presentations

3 that were made available this morning--and I'll just read

4 from the document. "After reviewing the data presented by

5 SmithKline Beecham and presentations by six independent

6 infectious disease specialists with arguments for and

7 against over-the-counter licensure, the panel members

8 reached consensus that there is no compelling reason to

9 oppose this OTC application for topical penciclovir. The

10 panel stated that this should not be viewed as blanket

11 approval for other applications for OTC anti-infectives but

12 rather concluded that topical penciclovir treatment for

13 recurrent herpes labialis is a unique situation that meets

14 OTC criteria. The nature of cold sores is such that it is a

15 non-serious, self-limiting condition that is easily

16 recognized by the patient. The lesions have been shown to

17 respond to topical application by this drug. The therapy

18 has been proven to be nontoxic, and the potential for

19 misutilization appears to be very low."

20 "The panel did not extensively review the efficacy

21 data but concluded that a 20 percent reduction in time to

22 healing of the lesions, together with reduction in the

23 duration of pain and viral shedding, while not clinically

24 impressive, were potentially important to patients who

25 suffer from this disease."

1 "The panel remained concern that the frequency of
2 resistance to this class of antiviral drugs could increase
3 with the use of OTC topical penciclovir, but at the present
4 time, the data available on acyclovir, at least for genital
5 herpes, do not indicate a trend in this direction and as
6 such do not merit rejection of the proposed application. In
7 several surveys, including the results of the International
8 Society for Antiviral Research Task Force, on herpes virus
9 resistance, the prevalence of acyclovir resistance has
10 changed little--0.1 to 0.3 percent--in the nearly 20 years
11 of use in the immunocompetent host." And that includes data
12 not only available through the Task Force but also through
13 Glaxo Wellcome.
14 "These acyclovir resistance estimates were not
15 available to the panel that rejected the oral acyclovir
16 proposal for genital herpes in 1995. In addition,
17 preliminary results from an independent mathematical model
18 suggest that a significant increase in resistance is
19 unlikely with implementation of OTC topical penciclovir.
20 Moreover, the limited effect that topical application of
21 penciclovir on the lips would play in influencing HSV-2
22 diagnosis, transmission and resistance was also viewed as an
23 important component of the discussion."
24 "The panel strongly recommended that approval of
25 this application be tied to a commitment by SmithKline

1 Beecham to fund extensive surveillance studies over the next
2 10 years to monitor resistance trends that might be
3 influenced by OTC topical therapy. Such studies should be
4 conducted by an independent institution such sa the Centers
5 for Disease Control or the ISAR Task Force and should
6 include longitudinal studies on patients who receive
7 repeated courses of the drug. Timely publication of these
8 studies should be mandatory. Furthermore, with OTC
9 approval, SmithKline Beecham should provide extensive
10 educational programs on appropriate use, i.e, for oral fever
11 blisters, to address the panel's concern that misuse of the
12 topical product for genital herpes in the OTC environment
13 could enhance the emergence of resistance."
14 "The panel's opinion that there is no compelling
15 reason to oppose the proposed OTC switch of topical
16 penciclovir for the treatment of recurrent herpes labialis
17 takes into consideration the appropriateness of cold sores
18 as an indication that can be easily recognized and self-
19 treated, together with the currently available data that
20 support the safety of topical penciclovir and the lack of
21 change in the prevalence of resistance. While resistance
22 remains a concern, continued surveillance will ascertain
23 whether the prevalence of resistance changes over time."
24 Thank you.
25 DR. BRASS: Thank you.

1 There appears to be, at least in my mind, a
2 contradiction in your recommendations, particularly the
3 penultimate paragraph, because you use words like "tied to"
4 and "mandatory" which are outside the purview to ensure it
5 actually happens. We have heard a commitment by sponsor to
6 partake in that, but in point of fact--and I am sure I
7 reflect their intent on December 1, 1998--there is no way to
8 ensure that happens. So if you are using words like
9 "mandatory," and there is no mandatory way to impose such a
10 structure, I am confused.
11 DR. WHITLEY: Okay. We firmly believe that
12 SmithKline Beecham should be forthcoming in making a
13 commitment both to the Food and Drug Administration as well
14 as to the users of penciclovir that a 10-year program should
15 be in place, and I'll let them address that in terms of
16 their recommendations later.
17 DR. BRASS: Okay.
18 Dr. Lipsky?
19 DR. LIPSKY: A quick question. The recommendation
20 comes out as a double negative--no compelling reason to
21 oppose.
22 DR. WHITLEY: Sorry. It should not be a double
23 negative.
24 DR. LIPSKY: But to be positive--well, no
25 compelling reason to oppose--I guess, grammatically, it is

1 probably not as eloquent.

2 DR. WHITLEY: How many "noes" can we get into a

3 sentence; right.

4 DR. LIPSKY: Was there a compelling reason to be

5 in favor of the switch?

6 DR. WHITLEY: No, no.

7 DR. BRASS: Dr. Masur?

8 DR. MASUR: That was my question as well.

9 DR. BRASS: Thank you.

10 Dr. Olivo?

11 DR. OLIVO: I have a question for Dr. Whitley.

12 Dr. Whitley, in terms of your recommendation that this be

13 tied to a surveillance program, how would you use the data

14 from such a surveillance program? Would you have a

15 preconceived notion of what data would--

16 DR. WHITLEY: I think that's a very good question,

17 because the question really focuses on what is the threshold

18 at which you would say resistance is becoming such an

19 egregious problem that the product should be withdrawn from

20 the market. That was brought up in the FDA presentation

21 this morning, and I think it was alluded to in Earl's

22 presentation although not stated explicitly.

23 Quite honestly, we did not put a percentage on

24 that. I think that if we got 3 percent or 5 percent and saw

25 that incidence continuing to increase over time incremental,

1 it would be of concern.

2 DR. BRASS: Dr. Yogev?

3 DR. YOGEV: You mentioned mathematical models. I

4 wonder if the model we saw today, the 5 percent, 12 years,

5 resistant one percent does not apply to the

6 immunocompromised, and in a population now that, because of

7 data transparent HIV and so forth, increase in those

8 numbers. I don't see anything in your statement of concern

9 to that specific effect, the increase in immunocompromised;

10 they are already there to do the 12 years.

11 DR. WHITLEY: We did not specifically address the

12 use of the medication in the immunocompromised host per se.

13 What we suggested was that there be a strong educational

14 message not to use the drug under such circumstances.

15 DR. BRASS: Thank you very much.

16 The next speaker is Dr. Stephen Sacks.

17 DR. SACKS: I'd like to thank the Committees for

18 allowing me to speak today.

19 [Slide.]

20 DR. SACKS: My name is Steve Sacks, and I am going

21 to talk today about some clinical perspectives and also try

22 to compare and contrast in a few short minutes what I see as

23 the issues related to this switch versus the switch of oral

24 acyclovir for herpes genitalis, on which I was a member of

25 the advisory committee and voted against it.

1 I work at Viridae Clinical Sciences, which I
2 founded five years ago. I am an infectious disease
3 physician and specialize in virological diseases, and I have
4 been practicing in the field of herpes for 20 years.
5 I am a professor of pharmacology and therapeutics
6 at UBC, a member of the Herpes Resistance Task Force that
7 Earl just talked about. My research interest has been in
8 herpes resistance--for example, we were the first to
9 describe the clinical relevance of viral heterogeneity that
10 was brought up this morning; we were the second to describe
11 a polymerase mutation from acyclovir resistance, the first
12 to characterize in vivo complementation and its role in
13 reactivation of resistance in HIV; and recently, we
14 characterized the homopolymer runs of g-strings and c-chords
15 that characterize the characteristic TK mutations that
16 result in resistance in HIV.
17 I was a consultant at the FDA Advisory Committee
18 for several years and participated in the OTC switch of oral
19 acyclovir, and again, I voted against it. I was a
20 participation in the follow-up IDSA Panel, which I am going
21 to refer to today and Rich has already talked about.
22 At Viridae, we run a contract research
23 organization and do pharmaceutical consulting. Unlike Rich,
24 I wish I had consulted for every, single drug company in the
25 world, but I have consulted for many and certainly most of

1 those that are involved in herpes simplex virus infections,
2 specifically, SmithKline Beecham which I have specifically
3 worked with in the process of the OTC switch, and so I am
4 directly conflicted in that regard. I have no financial
5 interest or gain from the vote, however.
6 I did the same for Glaxo Wellcome, actually. I
7 have also worked with Bristol Meyer Squibb on mabucavir
8 [ph.] and Lidac [ph.] on its labialis product and on
9 other herpes antivirals and OTC matters over time.
10 Next slide.
11 [Slide.]
12 So, what were the issues raised by the FDA in the
13 IDSA when considering the OTC switch of oral acyclovir for
14 recurrent herpes, and are the issues the same--I mean, why
15 is denavir different, or why is it the same--and how do
16 these issues really impact the benefit-to-risk ratio, which
17 is really the bottom line.
18 Next slide.
19 [Slide.]
20 So the things that were brought up by the FDA and
21 followed up by the IDSA, a few were mentioned this morning
22 by the FDA--I think they listed three of them--the list is
23 as follows that was brought up in publications.
24 One was self-diagnosis and misdiagnosis, which is
25 really my key concern. Educational initiatives were a

1 concern; counseling and STD screening; asymptomatic shedding
2 and transmission; misuse in general, but also in pregnancy;
3 individual safety; accessibility in cost; labeling;
4 precedence--in other words, what are we doing here; and
5 public safety, specifically with regard to resistance.
6 Next slide.
7 [Slide.]
8 I just want to remind the panel and everybody in
9 the audience that when we talk about OTC switch
10 considerations, and as a previous member of a committee
11 doing this, it is very difficult to hang onto the fact that
12 we are only considering the issue of the switch and not the
13 issue of the drug itself and its impact potential on
14 resistance. Certainly, antivirals do cause resistance in
15 some situations. You have heard the numbers. You have
16 heard that they are not changing and so on. And obviously,
17 these anti-herpes viral drugs are sometimes life-saving, so
18 if there were obviously going to be an impact that would
19 change the ability to use life-saving drugs, we wouldn't
20 want to do it.
21 But today we are considering only the issue of the
22 switch to the OTC.
23 [Slide.]
24 In my opinion, the issues differ significantly
25 from the concerns raised with oral acyclovir for chronic

1 suppression of recurrent genital herpes. First, this is
2 topical; secondly, it is acute therapy, not chronic therapy,
3 and therefore, the exposure is localized and episodic. It
4 involves the lips and not the genitalia, and it is not an
5 STD.
6 These are considerable differences, but there are
7 some parallels as well.
8 [Slide.]
9 In regard to self-diagnosis and misdiagnosis, this
10 list was made by the panel.
11 [Slide.]
12 If the physician is removed from the decision
13 loop, will the diagnosis really be missed? No. Doctors,
14 first of all, don't use the diagnostic test to test for
15 labialis in reality. Secondly, look in the mirror--it is
16 visually obvious--a cold sore.
17 Genital herpes, on the other hand, is a complex
18 diagnostic issue involving serology, counseling, and so on.
19 No co-infection testing is appropriate. I was
20 very concerned on the panel that people with STDs would be
21 missed for their chance to be detected for HIV and so on.
22 And of course, physical examination is pretty much
23 irrelevant with cold sores.
24 Next slide.
25 [Slide.]

1 And furthermore, my colleagues are notoriously bad
2 at treating labialis. We often use systemic medications
3 where in fact they are not indicated, and a lot of
4 situations arise where there is mistreatment anyway by the
5 physician. And really, the severe and refractory ones are
6 going to wind up in the doctor's office anyway.
7 Next slide.
8 [Slide.]
9 Educational initiatives--in fact, these are
10 significantly potentiated with OTC switch, in my opinion.
11 First, patients have an opportunity to learn more about
12 diagnosis, about treatment, and also about prevention
13 strategies. One of the big problems we have in genital
14 herpes management now is the oral-genital transmission
15 increase because people don't ever use safe sex for oral-
16 genital sex--not "ever," but very rarely--and as a result,
17 we are seeing a large increase in Type 1 genital herpes.
18 That is an educational flaw which could in part be resolved
19 through this.
20 Next slide.
21 [Slide.]
22 Counseling and STD screening--in fact, counseling
23 by the physician is minimal in labialis. It really just
24 isn't happening. This provides an opportunity now with
25 educational materials to accompany OTC things that might

1 actually improve things. And of course, STD screening here
2 is not relevant.
3 Next slide.
4 [Slide.]
5 What about asymptomatic shedding and transmission?
6 In fact, educational intervention is potentially enhanced by
7 the switch to OTC, which might actually involve transmission
8 and could, as I just talked about; but in fact, asymptomatic
9 shedding is not directly impacted because this treatment is
10 episodic. So, unlike the concerns of resistance in HIV,
11 where you have poor compromised host status, and you also
12 have continuous pressure on the virus which is continuing to
13 try to replicate under the pressure of drug, this is not
14 what is happening in this situation.
15 Next slide.
16 [Slide.]
17 What about misuse? A lot was brought up by the
18 FDA this morning about misuse, but I want to try to put some
19 of this in clinical context. First of all, if you misuse
20 this drug, maybe on acne or impetigo or chapped lips--so
21 what? It's not the best thing in the world, but in terms of
22 clinical relevance, it probably isn't. It is a small tube,
23 it has a small brand name and indication, and there really
24 are no significant AEs that anybody can think of why or have
25 seen in any clinically relevant situation with this drug.

1 There is clear labeling, and still some misuse
2 occurs. But in my opinion, the misuse issue--there is
3 always going to be some, and there is always going to be
4 some misgiving. But the question is where should you learn
5 about how to correct it, and actually, we are going to learn
6 a lot if we have the opportunity to license this product and
7 actually learn through the process of evolving this in the
8 marketplace, which is really where the learning process
9 could take place, because the impact or likelihood of
10 concerns that has been raised so far is very small.
11 Next slide.
12 [Slide.]
13 What if it is used to treat herpes genitalis? A
14 lot was brought up about this. First of all, the efficacy
15 is not determined, but this drug is probably effective in
16 the treatment of genitalis. I mean, if you are guessing
17 what is going to be the outcome, the outcome of this drug in
18 labialis was almost the same as the outcome of famvir in
19 genitalis, which is actually a very effective drug. So if
20 it were used episodically, it isn't what we would like
21 people to do, because they wouldn't be seeing the doctor,
22 but it is different, because the misuse does not equate with
23 approving an OTC product for genitalis. It is going to be
24 the occasional patient; it is not going to be recommended,
25 and there will be occasional patients who will miss the

1 system with the doctors, too.

2 Next slide.

3 [Slide.]

4 What about misuse in pregnancy? Well, you have

5 heard the data that this drug just simply isn't absorbed to

6 enough of an extent that it could be relevant. In fact,

7 famvir has been used accidentally in pregnancy many times,

8 and so far, there has been no hint of a problem with that

9 drug.

10 Next slide.

11 [Slide.]

12 Individual safety--well, in fact, very large

13 cohorts are exposed, and so far, this clearly looks

14 clinically safe, and in fact, unlike some other products

15 already on the market, it lacks SLS, which is an irritating

16 product.

17 Next slide.

18 [Slide.]

19 Accessibility and cost were brought up by the

20 committee, and in fact, there may be some loss of coverage

21 from this, I suppose, because of the Rx-to-OTC change. But

22 in fact in doing so, unlike with genitalis, you aren't

23 taking a patient who may become dependent on the drug for

24 psychosocial survival and pulling them off suppressive

25 therapy. That is not what is going on here. I think it is

1 legitimate to make this a consumer-driven issue.

2 Next slide.

3 [Slide.]

4 Labeling--well, you have talked about a lot of the

5 problems, and I am not going to go into them, but I think

6 the perfect label can evolve and should evolve in the

7 marketplace.

8 Next slide.

9 [Slide.]

10 Precedence--well, the precedence concerns with

11 oral acyclovir were the first systemic antimicrobial over-

12 the-counter, and this is, of course, not in that category.

13 It was also raised that it was the first OTC for an STD, and

14 this is not in that category, either. So applicability to

15 topical for labialis is really only related to the potential

16 for misuse as an STD treatment or potentially in the

17 compromised host.

18 And as an STD treatment, while this is not the

19 preferred route, there is really no hypothetical down side

20 for the occasional user. And certainly we need to pay

21 attention to not using it in a compromised host.

22 Next slide.

23 [Slide.]

24 Public safety and resistance, I'll just quickly

25 talk about. Specifically, will resistance develop?

1 Acyclovir experience, as you know, is at a low level and
2 hasn't changed. We worried a lot at the FDA panel a few
3 years ago about TK-negative strains and were told they were
4 not virulent. It turns out some of them are. Has this
5 really been a problem? Well, as all the speakers have
6 stated, the issue with the competent host is what difference
7 does it make--you clear the virus when you treat it with
8 water--so you are going to clear it if you treat it with
9 something, and it develops short-term resistance.
10 Obviously, surveillance is essential.
11 Next slide.
12 [Slide.]
13 With compromised hosts, the only ones who are
14 getting trouble with resistance are those with very low CD-4
15 counts, and in fact, clinically, it seems as if the
16 incidence is really decreasing, not increasing. The vast
17 majority of patients who are severely compromised are
18 already on these drugs systemically, either orally or I.V.,
19 especially in the transplant oncology group, and the
20 resistance does develop--it has been 5 percent for years--
21 but an occasional topical misuse, just in terms of
22 perspective, clinically, it just seems hard to really buy
23 that that is going to make a significant difference. And of
24 course, these tubes are so small, and you see these patients
25 who are severely compromised, with these big, necrotic

1 lesions the size of a grapefruit--they are going to have to
2 buy a lot of tubes to fill up the hole, and it just seems
3 clinically not that likely that it is going to be that big a
4 problem.
5 Next slide.
6 [Slide.]
7 So why is resistance within a competent host--you
8 know, actually, these drugs work by something called
9 substrate specificity, as Dr. Levin outlined, and it is
10 unique to this class of drugs. What is important about that
11 is that it doesn't apply to bacteria, it doesn't apply to
12 other viruses, it doesn't apply, actually, to any other
13 anti-infective situation. Indeed, it is neutral to
14 everything that is not herpes or zoster. We worry about
15 vancomycin, where we didn't see any resistance, and all of a
16 sudden, we did. But with vancomycin, for example, we
17 continuously exposed the gut, which is full of bacteria, to
18 this drug over a period of years. With topical on a cold
19 sore, first of all, you aren't exposing anything but the
20 skin; and secondly, the organisms are neutral to this that
21 might be exposed anyway. So it is not like there is a
22 continuous flora of herpes in the gut.
23 Furthermore, there is a self-limited shed period,
24 and the short exposure reduces the potential for both
25 resistance and transmission.

1 Next slide.

2 [Slide.]

3 So topical benefit, in my opinion, in summary
4 presents unique issues for consideration in the switch. The
5 oral acyclovir concerns for genital herpes do not apply
6 except for off-label misuse and potential for resistance.
7 Unfortunately, nobody can write you a promise that says we
8 will never, ever see a problem with resistance no matter
9 what; it is always possible, and it always will be possible
10 that sometime in the future, no matter how much data we have
11 gathered, that that might happen. However, it has been
12 shown to you in many situations that the chances are low.

13 In addition, on the benefits side of this
14 equation, we see increased educational potential, the
15 potential for prevention because of education, access early
16 so there is relevance to treatment, probably reduction of
17 health care costs and doctor visits, and the psychosocial
18 impact might also be improved.

19 Next slide.

20 [Slide.]

21 Finally, I would say that in my opinion, denavir
22 safety, potential for misuse causing harm, and risk of
23 resistance affecting the public health are exceedingly
24 unlikely to be altered by a change. If there is a place for
25 the OTC switch of any antiviral, like the Committee said, as

1 Rich summarized, this is probably the most logical first
2 step. It is a unique situation, as they said.
3 Surveillance is in place, and it is satisfactory.
4 Further, we stand to gain from what will be learned in the
5 marketplace. The Resistance Task Force will learn how to do
6 the proper surveillance and how to make the labs uniform.
7 These are all things that can't be expected to be known in
8 advance of having the problem to study. We need to have the
9 opportunity to look at this.
10 In fact, the public benefits from the switch are
11 pretty clear. The risks, in my opinion, are really quite
12 theoretical, and the theory points to a very small risk.
13 Thank you.
14 DR. BRASS: Thank you.
15 Dr. Masur?
16 DR. MASUR: While you have that last slide up,
17 what would you say the public benefit is when you say they
18 are "clear"?
19 DR. SACKS: I mentioned on the last slide that I
20 think the benefits side includes improved education. I
21 don't think you can--
22 DR. MASUR: I realize that, but in terms of the
23 course of the disease, your opinion is that the--
24 DR. SACKS: I didn't really mention much about the
25 course of the disease. I think the issue here, from my own

1 perspective, is regarding course. I kind of agree with Rich
2 in his summary of the Panel, which is that it is not
3 compelling that the clinical benefits of this drug are so
4 dramatic that it is going to improve the public health to
5 that degree. On the other hand, there are improvements, and
6 it is the first drug that has been shown--and I think that
7 in a consumer-driven society where there are benefits that
8 make people feel better and relief psychosocial issues and
9 so on, that those are real, and they should not be too
10 minimized, either.
11 So I see this more as an issue of benefit by
12 choice rather than by--I don't believe that in the absence
13 of the other benefits like improved education, access, more
14 information about resistance and so on, that there is a
15 widespread public health improvement by approval of the
16 drug.
17 DR. MASUR: And you think the education is going
18 to come by the fact that patients will read the package
19 insert?
20 DR. SACKS: I think that patients do--actually,
21 they have quit good data on the fact that patients do read
22 these package inserts. I have seen that at some point. I
23 don't have the data at my fingertips. But it is striking--
24 most of what I do is with regard to genital herpes, and in
25 Canada, we are seeing almost 50 percent Type 1 as a first

1 episode, and almost down to the last individual who gets
2 that, they are shocked that most of them have had oral-
3 genital contact with someone with a cold sore--90 percent of
4 them--and most of them had no idea that there was any
5 infectious basis there. I think that is a huge potential
6 advantage.
7 Also, I think the whole field of herpes simplex
8 virus treatment is moving more toward the consumer. For
9 example, my current recommendations for genital herpes would
10 say that suppression safety has been demonstrated well
11 enough that largely, we should be using suppression much
12 more than we have in the past and that most of the choices
13 around suppression should probably be based on things like
14 lifestyle and choices of the patient in terms of how much
15 the impact of these infections are affecting their lives.
16 And I think denavir fits--to a lesser extent, obviously--but
17 in that same model, which is that you give the patient a lot
18 of power and a lot of good response that has to do with just
19 being able to take choices that do something.
20 The other point is that there are 12 or 15 OTC
21 products for labialis in every drug store, being advertised
22 and blitzed. One of them is Heparin, one of them is Phenol,
23 one of them is topical anesthetics. Now, you have
24 everything under the sun, and none of them works; 100
25 percent of them are snake oil.

1 We have now the first product that finally works,
2 that wants to also be sold in the way people are used to
3 buying drugs, and we are saying to them, wait a minute,
4 there are all these concerns. But really, I am just saying
5 the concerns are a little bit--from a clinical perspective,
6 I think the concerns that have been raised this morning are
7 understandable, they all need to be watched, but really,
8 using that to prevent going forward seems a little bit
9 overkill to me.
10 DR. BRASS: Ms. Hamilton?
11 MS. HAMILTON: A quick question. If consumers
12 misuse this product and use it for treatment of genital
13 herpes, is there a health risk posed for that consumer
14 because of the way in seeking appropriate medical treatment?
15 DR. SACKS: People with genital herpes should seek
16 medical treatment, and yes, there would be a concern if
17 somebody delayed going to the doctor for any reason. I
18 guess the question clinically is would access to this
19 product--it would be hard for them to figure out that it is
20 for genital herpes the way it is being set up; it has a
21 unique name and so on, and it requires a lot of knowledge to
22 know that they are even the same virus--so my clinical
23 impression is that it is pretty unlikely that that is going
24 to impact very many people that way. There are so many
25 other things that delay going to the doctor. First of all,

1 it is hard to get to see the doctor, anyway. there is money
2 for access. Most of it has to do with embarrassment and
3 shame. And if denavir were being sold and it were said this
4 is a treatment for genital herpes, I would be the first one
5 to stand up against it, believe me. I definitely think that
6 that should never happen. I don't think STD drugs should be
7 marketed OTC, not in the current era. But do I think the
8 potential for occasional misuse justifies blocking it? I
9 don't see it as--no.
10 DR. BRASS: Thank you, Dr. Sacks.
11 Our next speaker is Dr. Penelope Hitchcock.
12 DR. HITCHCOCK: Good afternoon, and thank you for
13 the opportunity to address the panel about this very
14 important issue.
15 I am the Chief of the Sexually Transmitted
16 Diseases Branch at the National Institute of Allergy and
17 Infectious Diseases. The mission of my Branch and our
18 Institute is to conduct research that will ultimately impact
19 on the health of the public. Our particular concern is
20 viruses involved in sexually-transmitted diseases.
21 Now, you might ask yourself why is this woman here
22 today concerned about denavir and cold sores. First of all,
23 herpes simplex viruses are rather egalitarian. The affinity
24 for one set of mucus membranes over another--in other words,
25 oral versus genital infections--is really probably a

1 carryover from days when we couldn't tell these viruses
2 apart very readily. It is very clear that herpes simplex
3 virus can infect either the oral mucosa or the genital
4 mucosa, regardless of whether it is HSV-1 or HSV-2.
5 So I worry a lot about HSV-1. In adolescent
6 populations, in a number of surveys that have been done
7 recently, one-third of genital isolates are oral HSV-1's.
8 We tell kids to have safe sex, and they think that that
9 means either use condoms, or masturbate, or have oral sex--
10 they are doing all of the above, and we are seeing a lot of
11 transmission from oral mucosa to genital mucosa.
12 So this is my business, and in fact I think we
13 have a very serious question in front of us and a very
14 important opportunity.
15 I want to do two things, part of which I'm sure
16 repeat some things that have been mentioned by others. I
17 want to talk about switch issues, and I want to talk about
18 compelling reasons for considering positively the request in
19 front of you.
20 First of all, I think it is very tempting to get
21 off the switch issue. One starts to worry about efficacy,
22 for instance. Well, the fact of the matter is that FDA made
23 a decision about efficacy without respect to this product a
24 number of years ago. It is effective; it is effective
25 enough to write a prescription for, and it reduces the

1 length of time of the lesion, in other words, increases the
2 rate of healing, and so efficacy is not the issue in front
3 of us. That will not change whether or not the prescription
4 is written or the drug is purchased in the drug store.
5 The safety issues--again, there is a huge
6 literature on the safety of this viral-specific drug. Its
7 mechanism of action is actually amazing in that it is one of
8 the very few drugs we have that specifically works on a
9 viral enzyme and not on a human enzyme, and that isn't going
10 to change regardless of where we purchase this drug or how
11 we get it.
12 And the indication for cold sores I think is an
13 interesting one. First of all, i is one of the few
14 conditions where I would imagine that close to 100 percent
15 of the people who suffer from cold sores feel fairly
16 confident about self-diagnosing, and I would say probably in
17 80 to 90 percent of the cases, these people are right. Even
18 in the physician's office, we do not bother to confirm a
19 diagnosis.
20 As mentioned by Dr. Sacks, we have a lot of
21 products out there claiming a spectrum of activity for cold
22 sores that you can buy cheaply or expensively in the
23 drugstore, none of which work. This product obviously does
24 have an impact on the rate of healing, and therefore, it is
25 separate from the products that are currently involved in

1 OTC purchase.

2 The other issue that is raised often here is drug
3 resistance, and I would argue that it too is not a switch
4 issue. Hear me out. We have an unprecedented problem in
5 front of us in terms of the spread of herpes infections,
6 HSV-1 and HSV-2. I would argue that probably 50 percent of
7 the people in this country, and probably 70 percent of the
8 people in this room, have either HSV-1 or HSV-2 infection,
9 and there is absolutely no indication that this is slowing
10 down--none.

11 For those of you who are physicians, I would ask
12 you: If a patient came to you with cold sores and asked for
13 a prescription for either a topical or a systemic antiviral,
14 an acyclovir-related drug, would you write that
15 prescription? Would you hesitate for a second to write that
16 prescription based on the concern of drug resistance?

17 I would guess most of you would not hesitate to
18 write that prescription, and although we all think and worry
19 about drug resistance a lot, if we agree that there are
20 medical indications for using more of this kind of drug, and
21 we followed through with that, we would be using a lot more
22 of this drug. And rather than worry, frankly, about the
23 development of resistance, which I would argue is ultimately
24 inevitable based on just the biology of the situation,
25 rather than worry about isolates and HSV-1 or HSV-2, I would

1 rather take that money, to be honest with you, and put it
2 toward a full court press to develop new types of drugs, new
3 categories of drugs, for this kind of infection--not
4 thymidine kinase inhibitors, but some other mechanism--
5 because ultimately, I think we will have this problem.
6 We worried about it to the extent that we funded
7 the research that was mentioned earlier, Sally Blower's
8 elegant studies on modeling, and we are continuing to fund
9 Sally and have asked her to look at what kind of impact we
10 might expect with a product like denavir if it were applied
11 to cold sores and reduced shedding by, say, one day. We can
12 model that. So we are very worried about it, and I don't
13 want to trivialize it, but I would say in the face of this
14 epidemic, we should be using more of these drugs. I happen
15 to think that chronic suppressive therapy is a very
16 important way to think about use of these drugs. So again,
17 I don't think resistance is a switch issue.
18 One of the members of the panel has asked two or
19 three speakers about compelling reasons to approve the
20 request in front of you, and I want to focus on that because
21 I think there are compelling reasons to approve this
22 product. And it doesn't have to do so much with the fact
23 that this is the best product in the world--I wish to heck
24 it were a better product; I would not have any reservations
25 about the position that I take in front of you today.

1 I think the partnership between the government and
2 the private sector in terms of commercialization of products
3 is absolutely key for us to have the tools to deal with
4 infectious diseases and other medical problems. And when I
5 look sort of longingly at what the commercialization of
6 certain kinds of products has resulted in in terms of
7 consumer education and use, I feel very sad that we have not
8 been able to mobilize that energy to deal with this kind of
9 problem.
10 How many families do you think realize that they
11 transmit HSV-1 infection to their infants and children? I
12 would bet that most people don't even recognize this is a
13 viral infection let alone something loving parents or
14 siblings are transmitting in the context of their families.
15 If you look at the data, most children are infected by the
16 time they are going off to school, and that infection rate
17 increases.
18 I think that that in and of itself would result in
19 behavior change that would begin to decrease the incidence
20 of infection. I think that we need to make strong
21 recommendations and set high standards. The National
22 Institutes of Health and the Centers for Disease Control
23 need to partner with people inside companies like SmithKline
24 to help develop educational materials and then to do post-
25 marketing studies to test them and see whether or not they

1 are effective, whether or not they are working.

2 That is a commitment that I take very seriously,

3 not with this company and this product, but any company that

4 has a product that ultimately is going to reduce the spread

5 of the disease or decrease the impact of the disease.

6 Today is World AIDS Day. As a matter of facta,

7 right now, there is a luncheon that is probably ending at

8 the White House. Ladies and gentlemen, we have had

9 virtually no impact on the spread of HIV in the world, we

10 really haven't. I think that what has happened in any place

11 where we have seen infection rates level off has to do with

12 something other than what the government has done, frankly.

13 It has to do with communities, it has to do with committed,

14 educated people who recognize what behavior changes they

15 could take to reduce infection even before we had the data

16 to support it.

17 In this country, HIV is in high-risk groups for

18 the most part--gonorrhea, syphilis, trichomoniasis--these

19 are the "brothers and sisters" of the disease of HIV

20 infection. They are in high-risk populations. This is not

21 true for HSV. HSV is a ubiquitous disease like human

22 papilloma virus infection. And when I ask myself what is

23 going to stop the spread of HIV, and in ten years, I am

24 standing up at a podium, why HIV is going to be any

25 different from genital herpes, I don't have an answer.

1 There is absolutely no reason why it is not going to spread.
2 We have done the experiments with HSV. I think we
3 have an opportunity to put in the hands of people a product
4 that is safe, more effective than anything else, and will
5 provide an educational opportunity that we really need, that
6 we desperately need.
7 With that, I'll conclude and answer any questions,
8 but I really think there are compelling reasons to look at
9 this in a very positive way.
10 Thank you.
11 DR. BRASS: Dr. Lipsky?
12 DR. LIPSKY: Can you cite some examples of OTCs
13 and their promotion that have been effective in educating
14 the public or in improving the public health?
15 DR. HITCHCOCK: I think Zantac is a really
16 interesting example. We obviously sell it over-the-counter
17 at a lower concentration than we prescribe it, but now
18 people who have heartburn, who suspect they have an ulcer,
19 can go and get either Zantac or Pepcid-AC.
20 But if you think about it, the symptoms of
21 indigestion or ulcers or whatever it is are not papinumonic
22 [ph.] at all. We could be looking at an infection. We
23 could be looking at helicobacter pylori infection. We could
24 be looking at stomach cancer that is ulcerated. We could be
25 looking at symptoms of heart disease. But the fact of the

1 matter is we have an educational campaign associated with
2 Zantac; people can think about this, they can take it, and
3 if their symptoms don't alleviate, I think they are more
4 likely to go to the doctor. And in fact there has been an
5 awareness of medical conditions that--I mean, we cannot for
6 the most part reach individuals otherwise.
7 DR. LIPSKY: I am just curious--what you have just
8 said has been documented in a study, or is there hard data
9 on what you have said about increased public awareness of
10 diagnosing other GI conditions?
11 DR. HITCHCOCK: In other words, have we done
12 research to look at--
13 DR. LIPSKY: Not necessarily you or your branch at
14 the NIH, but has anybody--can I go to the literature and
15 find a substantiation of that statement?
16 DR. HITCHCOCK: I'm not sure that you could. I
17 am sure that you could in fact ask people about Zantac and
18 Pepcid. Why don't you do the experiment when you go to
19 dinner this evening, and ask a couple of people about this
20 product? I think that once you have television commercials,
21 once you have testimony and advertising, you begin to
22 increase awareness in a way that you don't otherwise. It is
23 personal opinion, I grant you, but I think it makes a lot of
24 sense.
25 DR. BRASS: Dr. Masur?

1 DR. MASUR: Just to be consistent and ask all the
2 speakers a similar question--one thing I was intrigued
3 about--you made a lot of telling points, but when you were
4 talking about topical acyclovir and topical penciclovir, you
5 suggested that when patients come to physicians, the
6 physicians readily prescribe this because they think it is
7 effective. Are you suggesting that for either genital HSV
8 or oral HSV, you would recommend topical rather than oral
9 therapy, that that is a recommendation, or that physicians
10 should be doing that?
11 DR. HITCHCOCK: Not at all, and I am sorry if I
12 misspoke. What I tried to ask you is if a patient wanted an
13 ointment to put on cold sores whether you would be reluctant
14 to prescribe that ointment to them based on a concern of
15 drug resistance. My guess is that you would perhaps tell
16 them about other products as well, because we all know that
17 the data on systemic treatment is more impressive than on
18 topical treatment.
19 DR. MASUR: Right, but you are not recommending
20 that a physician prescribe that if he thinks there is a
21 better drug, just because the patient requests it?
22 DR. HITCHCOCK: No. I am trying to say that we
23 would not hesitate to write a prescription based on a
24 concern of drug resistance, and this is simply an example of
25 increased use that is indicated because of a condition.

1 DR. MASUR: I have to say that concern of drug
2 resistance is a major reason not to write prescriptions--
3 maybe not with this drug, but as a general principle, that
4 is a major issue that we hope all health care professionals
5 are eminently aware of.
6 DR. HITCHCOCK: Don't misunderstand me again. I
7 don't disagree with you. But if you have a condition with a
8 known etiology, whether you have actually done the diagnosis
9 or not, let's assume that as a physician, you are going to
10 think in your mind that this cold sore is caused by HSV, and
11 you know the drug is specific, then my guess is you would
12 write a prescription. This is not an indication of a sore
13 throat and you don't know what is causing it, or an abscess,
14 and you don't know what's causing it. This is a link that
15 you would make, and you probably would not refuse to write
16 this particular prescription based on a perception of drug
17 resistance concern.
18 DR. BRASS: Thank you, Dr. Hitchcock.
19 We now have two letters that were submitted for
20 presentation at the open public hearing. Unfortunately, I
21 do not have conflict of interest information on either of
22 the individuals who have submitted these, and I will ask Dr.
23 Titus to read them.
24 DR. TITUS: The first letter is from Donald M.
25 Coen, from Harvard Medical School, Department of Biological

1 Chemistry and Molecular Pharmacology.

2 He writes to the Committee: "I am writing to
3 comment on the new drug application regarding over-the-
4 counter topical penciclovir which goes before your Advisory
5 Committee on December 1, 1998. I have worked for about 18
6 years on drug resistance in herpes simplex virus. Although
7 I have consulted for SmithKline Beecham in this area, I
8 oppose approval of OTC penciclovir."

9 "Drug resistance is not an all-or-none phenomenon
10 like resistance to some antibacterial drugs. There is a
11 broad spectrum of penciclovir-resistant mutations, with
12 varying effects on susceptibility and on pathogenicity of
13 the virus in animal models. There clearly are penciclovir-
14 resistant mutants that, based on laboratory studies, retain
15 both sufficient resistance and sufficient pathogenicity to
16 be clinically relevant. We have documented an HSV mutant
17 which is penciclovir-resistant that arose in a patient,
18 established latency, and then reactivated, even in the face
19 of high-dose acyclovir." And he has a publication as
20 "Horsburgh et al in the Journal of Infectious Diseases,
21 167:618, 199."

22 "Modeling studies such as that published by Blower
23 et al. (Nature Medicine 4:673, 1998) indicate that
24 widespread use of an anti-HSV drug will lead to increased
25 prevalence of resistant mutants. The frequency of

1 resistance may be relatively low, but given the large
2 numbers of people who may take the drug, the numbers will be
3 relatively large. Resistant mutants that arise are likely
4 by selection to be those that retain pathogenicity."
5 "There are several important concerns specifically
6 relevant to OTC penciclovir. Although the proposed
7 treatment is topical, resistant virus selected in peripheral
8 tissues of a patient may establish latency in the patient or
9 in the patient's contacts. OTC status will make it more
10 likely that patients will take suboptimal doses of drug, due
11 in part to concerns about cost, which will permit a larger
12 pool of replicating virus and select more for more
13 pathogenic mutants that are resistant enough to cause
14 disease in the face of drug. When disease persists, the
15 patient may escalate the doses, but will already have
16 increased the pool of replicating virus, increasing the
17 changes for continued selection of resistant pathogenic
18 viruses. Based on experience with other anti-HSV drugs, it
19 appears that relatively small decreases in susceptibility to
20 penciclovir are likely to be clinically relevant. Thus,
21 once resistance is established, appropriate dosing will not
22 eliminate the virus. Additionally, these concerns also
23 apply to genital herpes. Although OTC penciclovir is being
24 targeted for cold sores, it is highly likely that those with
25 genital herpes virus will use the drug."

1 "Almost all penciclovir-resistant mutants have
2 been cross-resistant to acyclovir. Acyclovir is especially
3 crucial in the immunocompromised, such as patients with
4 AIDS, to treat severe infections. The alternative drugs are
5 nowhere near as safe, effective or reliable. The increase
6 in convenience of OTC status for a very small (less than one
7 day) benefit to people with mild, self-limiting disease is
8 not sufficient reason to increase the number of patients
9 with severe acyclovir-resistant disease."
10 "I hope these comments are useful to the Advisory
11 Committee."
12 The second letter is from Michael Oxman, who is a
13 physician at the University of California, San Diego. He is
14 a professor of medicine and pathology.
15 He writes: "I am writing to express my strongest
16 opposition to the proposal to move topical penciclovir from
17 prescription drug to OTC status for the treatment of herpes
18 labialis. My reasons for opposing OTC status for topical
19 penciclovir are outlined below."
20 "Proponents of OTC status for topical penciclovir
21 for herpes labialis emphasize how little impact making this
22 drug available OTC will have on the prevalence of resistance
23 to penciclovir. Their arguments include: 1) the
24 manufacturer plans to package the drug in small tubes that
25 are, we are told, going to be relatively expensive.

1 Consequently, there is alleged to be less potential for
2 misuse and abuse."
3 "2) Problems of misdiagnosis and failure to detect
4 other STDs are not the important issue that they were with
5 OTC oral acyclovir for genital herpes."
6 "3) Modeling suggests that resistance would not be
7 a problem at all for 20 years or more under worst case
8 assumptions."
9 "4) It is asserted that viruses are not equivalent
10 to bacteria with respect to their potential to develop
11 resistance to antiviral drugs and have that resistance
12 selected for by widespread drug use."
13 "5) Surveillance has not shown any increase in the
14 proportion of acyclovir-resistant isolates of HSV in the 15
15 years since the drug was licensed."
16 "I totally disagree for the following reasons."
17 "First, OTC licensure of topical penciclovir will
18 establish a precedent that will make it difficult to resist
19 subsequent attempts to obtain OTC status for antivirals in
20 the future, even in cases where the risks and adverse
21 consequences are much greater than those associated with
22 topical penciclovir for herpes labialis."
23 "Second, viruses, including herpes viruses, are
24 just as likely as bacteria to develop resistance to drugs,
25 and just as prone to the selection of resistant mutants when

1 subjected to selective pressure. The suggestion that
2 selective pressure is less likely to result in a population
3 of drug-resistant herpes viruses than in a population of
4 drug-resistant bacteria is ridiculous. In the case of
5 herpes viruses, the presence of large numbers of latent
6 infections alters the population dynamics but not the
7 ultimate result."
8 Third, the surveillance data indicating that the
9 proportion of acyclovir-resistant isolates of herpes simplex
10 virus has not increased despite more than a decade of use of
11 this drug is a very misleading 'red herring.' Most isolates
12 of HSV obtained today reflect shedding of virus by latently
13 infected persons whose infections predated and/or were
14 independent of any use of acyclovir. Given the vast
15 reservoir of latent acyclovir-sensitive HSV, it will be some
16 time before the emergence of resistant virus is reflected in
17 the overall population of HSV isolates. By the time such
18 general surveillance detects an increase in the proportion
19 of resistant HSV isolates, large numbers of people will have
20 been infected with resistant HSV, with the establishment of
21 latent infections that make them lifelong shedders of
22 resistant viruses."
23 "In this sense, herpes viruses are different from
24 bacteria. Bacterial populations are dynamic; removal of
25 selective pressure results in a fairly rapid reversion of

1 the bacterial population to sensitivity. In contrast,
2 removal of selective pressure will not cause latent
3 infections with resistant HSV to become drug-sensitive, and
4 people who are latently infected with resistant virus will
5 continue to shed resistant viruses for decades."
6 "To obtain meaningful data, surveillance for
7 resistance should focus on people who are newly infected
8 following exposure to individuals who are being treated or
9 suppressed with acyclovir (e.g., 'discordant couples') like
10 those who have been studied to assess the efficacy of HSV
11 vaccines. This type of surveillance is not being done, and
12 the general surveillance that is being carried out is giving
13 us a false sense of security and providing data that is
14 being inappropriately used to support the assertion that OTC
15 status for anti-HSV drugs poses no risk to the public."
16 "Fourth, I am aware of no data on the effect, if
17 any, of topical antiviral therapy on asymptomatic oral
18 shedding of HSV-1, which appears to be the main source of
19 virus causing new infections, many of which occur in
20 children. I would think that reviewers would need to have
21 this information, including information on the possible
22 shedding of resistant HSV by treated persons, before
23 considering the question of OTC status for topical
24 penciclovir."
25 "Fifth, while 20 or 30 years may seem like a very

1 long time to some people assessing the biological cost of
2 uncontrolled use of antivirals, it is a short time
3 epidemiologically. Think of the emergence of MRSA, VRE,
4 penicillin-resistant pneumococci, and vancomycin-resistant
5 staphylococcus aureus. If actions taken 25 years ago could
6 have delayed their emergence and spread in the United
7 States, I am sure we would have gladly taken them."
8 "Sixth, how would we respond to a request to
9 approve OTC licensure of topical ampicillin or dicloxacillin
10 for pustules in the upper lip and nose? And just think,
11 development of resistance to penicillins and cephalosporins
12 would still leave us with vancomycin, gyrase inhibitors,
13 protein synthesis inhibitors, et cetera, whereas resistance
14 to penciclovir will deprive us of famciclivir, acyclovir,
15 valacyclovir, and every other nontoxic anti-HSV agent in the
16 pipeline."
17 "There are two other considerations. One, the one
18 study that demonstrated the efficacy of topical penciclovir
19 for herpes labialis showed statistical efficacy, but the
20 clinical efficacy was minimal. In fact, I suspect that not
21 many physicians are prescribing topical penciclovir for
22 herpes labialis, and the manufacturer hopes to increase
23 sales by promoting it directly to the public."
24 "Second, in deciding issues such as this, the FDA
25 should conduct a public health and welfare 'cost-benefit'

1 analysis. In the case of OTC penciclovir for herpes
2 labialis (versus its current status as a prescription drug)
3 the public benefit is virtually nil, and thus even the
4 smallest potential risk should lead to denial of the
5 application."
6 "Thank you for your kind attention."
7 DR. BRASS: Thank you.
8 That concludes the speakers in the open public
9 forum. Dr. Reeves from the CDC has also requested time to
10 make a statement.
11 DR. REEVES: The CDC has prepared a statement on
12 approval of over-the-counter penciclovir which I wanted to
13 read.
14 "Approval of topical penciclovir for over-the-
15 counter or OTC status will likely enhance patient
16 convenience to rapidly treat recurrent self-limited
17 orificial disease. However, potential public health
18 concerns must be considered. Major concerns involve
19 possible increase in the prevalence of resistant HSV-1 and
20 HSV-2 and less compelling concerns involve possible misuse
21 for other conditions."
22 With respect to HSV resistance, we have the topic
23 of HSV-1 and 2.
24 "There is little data on the prevalence of HSV-1
25 resistance to penciclovir. The recommended dosing schedule

1 is very two waking hours, which is not easy to achieve, thus
2 topical penciclovir use may result in suboptimal local
3 concentrations of the drug, possibly enhancing selection of
4 resistant HSV-1."
5 "With respect to HSV-2, it is possible that an OTC
6 formulation marketed for oral herpes will be used for
7 genital herpes. The multi-site acyclovir resistance study
8 conducted collaboratively by CDC and the Task Force on
9 Herpes Simplex Virus Resistance," which Dr. Kern presented,
10 "found that 0.3 percent of normal and 5.5 percent of HIV-
11 positive persons with genital herpes had HSV-2 isolates
12 resistant to acyclovir. There is essentially 100 percent
13 cross-resistance between ACV and penciclovir. Thus the rate
14 of ACV resistance could potentially increase with misuse of
15 penciclovir."
16 With respect to less compelling concerns of misuse
17 for other conditions, "OTC penciclovir may be misused to
18 treat orificial herpes in pediatric populations. Little is
19 known concerning the toxicity of penciclovir in children or
20 the cumulative effects of penciclovir exposure in pediatric
21 populations. Herpes simplex skin or mucosal infection in a
22 newborn requires systemic therapy which could potentially be
23 delayed by inappropriate use of an OTC product."
24 With respect to misuse in immunocompromised
25 persons, "Persistent, unusually severe or difficult-to-treat

1 herpes simplex infection may belie an underlying
2 immunodeficiency. It is conceivable that OTC treatment with
3 penciclovir could lead to delayed diagnosis of the
4 underlying condition."
5 To summarize CDC's statement, "Potential public
6 health concerns involve speculation about the behavior of
7 people who would use OTC penciclovir and the possible
8 resulting effects on herpes group viruses; empirical data
9 are not available on these points. Primary concerns involve
10 the possibility of an increase prevalence of HSV resistance
11 to penciclovir and related antivirals. These are long-term
12 cumulative public health issues rather than adverse effects
13 on individual patients using the formulation."
14 "CDC does not recommend for or against the
15 approval of penciclovir for OTC use for treatment of
16 recurrent oral herpes. However, penciclovir should not be
17 approved for OTC use until concerns regarding development of
18 drug-resistant HSV and potential misuse are addressed. The
19 measures outlined in the remaining recommendations would
20 help to address these concerns."
21 "Post-marketing surveillance for the emergence of
22 penciclovir-resistant HSV-1 and HSV-2 should be undertaken
23 by the company using methods developed with input from CDC,
24 FDA and other groups. Results should be reviewed with CDC
25 and FDA on a regular basis."

1 "Concerns regarding potential misuse should be
2 addressed through prominent, explicit labeling indicating
3 that a) use is for recurrent oral herpes lesions previously
4 diagnosed as such by a physician; b) this preparation is not
5 to be used to treat genital herpes; c) the drug is not
6 approved for use in children; d) if the condition persists
7 or is severe, a physician should be consulted, and e) the
8 drug is not for use in or near eyes or on the body."
9 "Post-marketing surveillance for misuse should be
10 undertaken for the company using methods developed with
11 input from FDA, with results provided to FDA for evaluation
12 on a regular basis."
13 "Finally, the company should voluntarily commit,
14 prior to approval, to immediately take corrective action up
15 to and including stopping the OTC marketing of penciclovir,
16 should the FDA determine that continued over-the-counter
17 marketing of this drug presents a risk to public health and
18 provides the company with the scientific evidence on which
19 it based that conclusion. (Note that this concept and this
20 wording were developed by the FDA Center for Veterinary
21 Medicine in July 1998 in connection with the approval of
22 Baytril 100, a fluoroquinolone antimicrobial, for use in
23 cattle.)"
24 Thank you.
25 DR. BRASS: Thank you.

1 Are there any questions for Dr. Reeves?

2 [No response.]

3 DR. BRASS: Thank you.

4 Next, I would like to ask Dr. Linda Katz, Deputy

5 Director of the Division of OTC Drug Products, to give us an

6 overview on the Rx-to-OTC switch process.

7 **Overview of Rx to OTC Switch Process**

8 **Linda Katz, M.D., M.P.H.**

9 DR. KATZ: Good afternoon. What I'd like to do in

10 the time that is allotted to me is to speak very briefly

11 about the prescription-to-OTC switch process. Basically,

12 what I'd like to do today is just focus on some of the

13 issues that go into the decisionmaking about whether a

14 product should switch from prescription to OTC status.

15 I am not going to describe any of the trials or go

16 through the efficacy data, even the usage oar the labeling

17 trials that we heard about earlier today, since that data

18 was presented, but again will talk more about the process

19 itself.

20 In addition, to wrap up, when I am finished, I

21 will go through the charge to the committee.

22 [Slide.]

23 Let me go through a little bit of a scenario,

24 since we heard about some scenarios earlier in the day, just

25 to again orient everyone's perspective.

1 When we are talking about prescription products,
2 prescription drugs are different from OTC drugs, and it is
3 important to keep some of the distinctions in mind. In the
4 first case, when we talk about a prescription product, we
5 paint the picture of patient who goes in to see a physician
6 or a health care practitioner with complaints related to a
7 specific disease or condition for which they would like to
8 have some kind of diagnosis made. The person is examined,
9 spoken to, things are discussed, tests are ordered, and the
10 practitioner will go ahead and write a prescription for a
11 product that they feel will treat the underlying condition
12 or symptoms that the person has walked in with.
13 The practitioner takes it upon himself or herself
14 to advise that individual who is the patient about the risks
15 and benefits of the drug, risks and benefits from different
16 treatments, and also to warn that individual about what kind
17 of side effects may potentially occur from using this
18 product as well as with any other product that they make
19 take concomitantly. The person who is involved is the
20 patient.
21 On the other hand, we have the OTC drug. In this
22 scenario, we have a person who walks into a drugstore, a
23 convenience store or a supermarket to look for a product to
24 treat some symptoms that they may have, albeit a headache,
25 heartburn or some symptomatology. They look around at the

1 shelves with a vast array of products, they pick up the
2 product, and the person makes the determination as which
3 product might be best to treat the symptoms that he or she
4 has walked in for. That person is a consumer and not a
5 patient.
6 It is important that I make that distinction for
7 you, which helps to go into some of the discussion that we
8 will need to have this afternoon, because that individual
9 who is the consumer needs to rely upon the labeling that we
10 have approved for that product to be able to use that
11 product effectively--to be able to know what the product
12 should be used for, what warnings are available, how often
13 the drug should be taken, and what medications, active and
14 inactive ingredients, go into that product when making the
15 decision to buy it.
16 Next slide.
17 [Slide.]
18 With that in mind, I'd like to shift again a
19 little bit and go through some of the definitions for
20 prescription to OTC switches. When I do this, I would also
21 like to caveat that there is a whole group of products out
22 there that are considered old drugs that are monograph
23 products that I am not going to talk about, because what we
24 are talking about are switch products themselves.
25 By definition, there are two kinds of products

1 that can switch from prescription to OTC status. One is the
2 complete switch, where the product that is currently
3 approved as a prescription product moves from the
4 prescription realm to the OTC realm. That is what is being
5 proposed here for the denavir topical product.
6 The other type of switch is a partial switch in
7 which part of the product goes over-the-counter and part
8 remains in the prescription world. Reasons could be a
9 certain indication would switch, a certain dose or strength,
10 duration of use, dosage form or route of administration or
11 target population.
12 One example of this would be when the ibuprofen
13 suspension products went from prescription to OTC, the
14 majority of the indications for fever and for analgesia went
15 over-the-counter. However, to treat juvenile rheumatoid
16 arthritis remains a physician diagnosis and a physician
17 treatment, and that portion remained Rx.
18 There is one additional--I am not sure we would
19 actually call it a switch anymore; in the past, we used to,
20 but we don't traditionally now--way that an NDA product gets
21 in the OTC world, and that is by having a lower dose of a
22 previously approved prescription product. For example, I'll
23 use ibuprofen. When ibuprofen went over-the-counter, it
24 went at a lower dose than was previously approved, but we
25 don't really consider it a switch per se because the 200

1 milligram ibuprofen tablet that one could buy OTC was never
2 prescription form.
3 Next slide.
4 [Slide.]
5 When one wants to consider what is appropriate for
6 OTC use, there are a variety of conditions that we look at
7 and go through with an application and with the sponsor when
8 they come to talk to us.
9 One is that the product has an acceptable margin
10 of safety. Is there a low misuse and abuse potential both
11 for the individual and for the population as a whole? Can
12 the consumer self-recognize and self-treat the condition
13 being proposed? Is the product effective for direct
14 consumer use, or to be used effectively does one need
15 specific monitoring or physician or health care practitioner
16 intervention, and can the product itself be adequately
17 labeled for safe and effective use?
18 Next slide.
19 [Slide.]
20 Efficacy itself, I will not talk about, because in
21 the switch product, one assumes that if the product was
22 approved Rx, and we are switching the product, that is was
23 effective. What I will focus on is safety, because that is
24 actually where the crux of the information that we depend
25 upon for an OTC switch comes from.

1 In terms of looking at the safety profile, one
2 needs to go back and look to see if there is sufficient
3 marketing experience to be able to characterize serious
4 toxicities, special toxicities of a class, and in particular
5 in this case what we are talking about are resistance issues
6 and also issues that will play into abuse and misuse that
7 might pose some potential toxicities for those individuals;
8 whether there is a margin of safety--and usually for OTC
9 use, we like a large safety margin just in case the consumer
10 does not use the product as prescribed; and any drug
11 interactions, both observed and potential.
12 Next slide.
13 [Slide.]
14 The sources of safety information come from a
15 revisiting of the prescription NDA database, going back to
16 look at the relevant clinical trials as well as looking at
17 any Phase 4 post-marketing studies that have been done. In
18 addition, any new trials that are presented in the NDA are
19 reviewed for safety, and safety information comes from other
20 sources--from published literature, from our own SRS
21 MedWatch database, and any foreign safety database, both
22 prescription and OTC, that might be available.
23 The crux, again, for an OTC product is its
24 labeling. That is critical to the successful use of this
25 product.

1 [Slide.]

2 Thus, in summary, when one wants to consider a
3 switch from Rx to OTC, these are again things that we need
4 to focus on--whether there is an acceptable margin of
5 safety, whether the adverse events can be clearly delineated
6 and easily recognizable by the consumer and are of such a
7 nature that the potential risks are worth the benefits. The
8 condition itself must be recognizable to the consumer, with
9 symptomatologies that can be improved. The condition or
10 therapy does not require significant monitoring or
11 intervention because if it does, it is probably better that
12 the physician or health care practitioner be the one to
13 administer the product so that correct monitoring and
14 intervention can be done. And the labeling must be clear,
15 such that a consumer can understand and follow directions.

16 [Slide.]

17 With that, I'd like to shift and go to the charge
18 to the Committees. In the first question that we will ask
19 the Committees to address after listening to all the
20 discussion and data that have been presented today, we would
21 like you to discuss the implications of OTC availability of
22 denavir on the prevalence of herpes simplex virus resistance
23 in immunocompetent and immunocompromised individuals.

24 For the second question, we would like you to
25 again address, based on the data presented, whether or not

1 you would recommend the approval of denavir for OTC use for
2 the treatment of herpes labialis in immunocompetent adults.
3 If no, what additional studies would you recommend? If yes,
4 we would like you to please discuss any additional Phase 4
5 studies, the design, conduct and monitoring of Phase 4 post-
6 marketing viral resistance and surveillance programs, and
7 any additional labeling comments, specifically for the
8 definition of "immunocompromised" in the label warning.
9 One additional comment I would like to make since
10 it came up in an earlier discussion is that we an ask for
11 Phase 4 post-marketing surveillance, however, again, it is
12 purely voluntary, and we cannot base approval on the fact--
13 some of this information may never come back to the agency,
14 and it is important that I make mention of that, that we can
15 ask for it, but it is really not a strict requirement.
16 With that, I'd like to end my comments and turn
17 the meeting back over to our chairman.
18 DR. BRASS: Thank you.
19 Are there any questions for Dr. Katz at this
20 point?
21 Dr. Woolson?
22 DR. WOOLSON: Would you mind repeating what you
23 just said about the post-marketing studies?
24 DR. KATZ: We can make it as a condition of
25 approval; however, once the drug is approved, we have little

1 regulatory status to make sure that all of this has been
2 completed in the way that we have asked for. It is agreed
3 upon at the time of approval, but again, there are a lot of
4 Phase 4 trials that we ask for that we just never get back.
5 DR. WOOLSON: Thank you.
6 DR. BRASS: Are there any other questions?
7 DR. MURPHY: I'd like to just clarify that, too,
8 for the antiviral committee. It does have a different
9 regulatory bite and gives us the capability to bring
10 something on the market [inaudible].
11 DR. WOOLSON: Thank you.
12 DR. BRASS: Thank you, Dr. Katz.
13 I anticipate have about another hour and a half to
14 two hours to go, so I'll ask for a quick show of hands if
15 anybody on the panel wants to take a break at this point
16 before we start the discussion or continue.
17 Any votes for a break?
18 [A show of hands]
19 DR. BRASS: Okay. We'll take a 10-minute break
20 and resume promptly at 2:45.
21 [Recess.]
22 DR. BRASS: Let's reconvene.
23 **Open Committee Discussion**
24 DR. BRASS: We will discuss the two charges posed
25 to us by the FDA individually. The first one will be to

1 "Please discuss the potential implications of d on the
2 prevalence of HSV resistance in immunocompetent and
3 immunocompromised individuals."
4 Since part of that issue revolves around exposure,
5 I'd like Dr. Marks to answer Dr. Lipsky's question of
6 earlier in the morning.
7 DR. MARKS: Actually, Ron Boon is going to go
8 through a couple of slides and talk about the answer to that
9 question.
10 DR. BRASS: Thank you.
11 DR. BOON: Thank you. My apologies for not being
12 very clear before, but we have used the computers and
13 hopefully tightened it up a bit in the break.
14 [Slide.]
15 DR. BOON: Going back to the briefing document on
16 page 102, where Dr. Lipsky mentioned the 600 kilos, this is
17 actually derived from the fact that there are an estimated
18 40 million people within the U.S. who have cold sores, and
19 if we were able to treat every, single one of those 40
20 million with 15 milligrams of penciclovir, this would result
21 in 600 kilograms of penciclovir usage annually, which would
22 equate to about 0.5 percent of the total anti-herpes drug
23 usage in the U.S. today.
24 If I could have the next slide, please.
25 [Slide.]

1 DR. BOON: Talking about the total usage of
2 antivirals in the United States today, there are currently
3 139,000 kilos estimated to be used of all antivirals both
4 systemically and topically. Of that, 1,400 kilos is for
5 topical usage--that's all nucleoside topical antivirals--of
6 which, this year, denavir constituted 10 kilograms.
7 [Slide.]
8 DR. BOON: If we move on to our predictions for
9 2002, it is predicted that the total antiviral market will
10 increase to 160,000 kilograms, systemic and topical. And
11 the portion of that topical part of that market in total
12 will decline to 947 kilograms, and the portion of denavir of
13 that would be 180 kilograms.
14 So I hope that is a little more clear a picture of
15 usage.
16 DR. BRASS: Dr. Lipsky?
17 DR. LIPSKY: Thank you.
18 DR. BRASS: Thank you very much.
19 Dr. El-Sadr.
20 DR. EL-SADR: I have another question to the
21 sponsor, if I could.
22 DR. BRASS: About this point or on something else?
23 DR. EL-SADR: Marketing--no?
24 DR. BRASS: Let's hold off.
25 What I'd like to do now is begin the discussion of

1 the first question and focus specifically on issues related
2 to resistance and factors that might influence our
3 assessment of resistance.
4 Perhaps, if I could begin by asking for a
5 clarification from the sponsor or their consultants. I was
6 confused about a couple of things. First, in terms of
7 estimating the prevalence of resistance using the
8 surveillance modalities, I was struck by many of the
9 comments which suggested it might underestimate the number
10 of actual percentage of viral particles that now bear
11 resistance.
12 In both your comments and your mathematical
13 modeling that was presented, you focused on establishing a
14 resistant strain within the primary host receiving
15 treatment. From my perspective, that doesn't seem to be the
16 major concern, but something that didn't even appear in the
17 mathematical model that was presented was transmission of
18 the resistant strain during a period of infectivity where an
19 unexposed host now becomes exposed to the resistant strain,
20 and the primary infection of that individual is with a
21 resistant strain. And it also seems, based on comments from
22 this morning, that that could actually occur in an initial
23 host that surveilled as being sensitive because of a low
24 prevalence of the mutated strain in that host. If that
25 happens to be the one that is transmitted during the

1 infectious process, the result would be an infection with a
2 mutated strain that is resistant to the organism.
3 If somebody could comment on whether my assessment
4 is accurate or not--Dr. Olivo?
5 DR. OLIVO: Let me just say that I think that that
6 is the dirty little secret about susceptibility testing, is
7 that you get an answer that doesn't tell you the answer to
8 the question your talking about, which is are there
9 resistant sub-populations that could be transmitted.
10 DR. MARKS: There are two pieces to that question.
11 One relates to the virology of that, and actually, Dr. Sacks
12 is one of those who put together most of the information in
13 the literature on the virology of that study, so I'll ask
14 him if he wouldn't mind commenting. Also, Dr. Leary from SB
15 might be able to add.
16 Then, in terms of how that interacts and how it
17 wasp ut into the mathematical model, we can also go back to
18 Dr. Lipsitch and see how that was interfaced. But we might
19 well start off with Dr. Sacks, since plaque autoradiography,
20 plaque reduction assays, he knows a great deal about.
21 DR. SACKS: Actually, I wanted to answer this
22 earlier, but I didn't have time, so I am glad you asked it
23 again. On the Resistance Task Force, we saw this initially
24 as one of our primary problems and one of the primary
25 issues, so several years ago we started a study, and the

1 study that we have now completed goes as follows.

2 We have been treating patients who are

3 immunocompetent hosts with recurrent genital herpes in three

4 groups. One is a group taking full doses, five tablets a

5 day, of acyclovir. The second group takes one tablet of

6 acyclovir and four placebo. And the third group takes

7 placebo. And we have been looking at plaque reduction

8 assays but also plaque autoradiograms on the first and last

9 isolates, so what we are looking for with plaque

10 autoradiography, because this is method of detecting viral

11 TK expression at the clone-to-clone level.

12 What we are finding is that we can detect changes

13 at about 6 or 7 percent of the population as opposed to 50

14 percent, which is what you see with plaque reduction, and

15 with that 6 or 7 percent, so far, we have found 100 percent

16 correlation with plaque reduction assay, actually. so that

17 in fact, we are not seeing sub-populations, and we are also

18 not seeing any resistance, or any change in susceptibility

19 or any change in plaque reduction proportions in those

20 immunocompetent hosts in the clinical trial, which was

21 statistically powered before it was set up.

22 The other question which was raised is a little

23 complicated, which is can you clinically acquire resistance,

24 and can that affect latency, and in fact brings up the issue

25 of in vivo complementation. In fact, we were the first, I

1 think, to describe in vivo complementation in HIV patients
2 in JID a couple of years ago. We had a patient who relapsed
3 with acyclovir-resistant herpes after drug pressure was
4 withdrawn, and she developed clinical and laboratory
5 resistance on an isolate subsequent to when she had stopped
6 antiviral therapy. It turned out that this was a mixed
7 population, as are many resistant isolates, but it was also
8 quite dominant, so the IC-50 was quite abnormal. But at the
9 same time, she actually refused antivirals and all
10 chemotherapy at that point--this was many years ago--and on
11 her subsequent isolates, and what we are finding in all
12 these patients who relapse with latent infection that seems
13 to have been acquired resistance is that actually, there is
14 so much pressure to revert to wild-type that that is exactly
15 what happens if you just leave the drug pressure off. And
16 in f act the opposite was stated here--I have forgotten by
17 whom--but that is not really true. The clinical sequelae
18 when you pull drug away--in Mike Oxman's letter, it said
19 that it's not true--in fact it is true that when you pull
20 drug pressure away. So far, even in severe HIV, where CD-4
21 counts are zero, we have seen a reversion to wild-type over
22 time.
23 The question is can you transmit this infection to
24 a partner, and yes, of course, you can transmit resistant
25 herpes to a partner. This has been document in the New

1 England Journal, and Steve Straus and Rhonda Cox
2 demonstrated this in one patient who was an HIV-infected
3 patient with herpes who became resistant on therapy and then
4 he had sex with an immunocompetent partner, transmitting
5 herpes but not HIV, and the partner acquired a mixed
6 population which was partly resistant. That has happened
7 once in 20 years.
8 Why would it happen only once? Well, there are
9 many reasons. First of all, breakthrough isolates--for
10 example, in famvir suppression studies with asymptomatic
11 shedding, we did a study of 180 women, and I think there
12 were 55 isolates that we got of patients who broke through
13 treatment and shed virus while on therapy, and they were all
14 susceptible in vitro, 100 percent of them.
15 So the chance of this happening still remains
16 quite low. But with labialis, I would put to you that the
17 patient has to not only apply it; it has to be during the
18 drug pressure application, and the patient basically has to
19 have mucocutaneous contact while there is an active lesion,
20 and which they know is an active lesion in treating with
21 topical creme. So there are many reasons why that is not
22 too common.
23 In suppression, you would think that that might
24 happen at some point in the future because of asymptomatic
25 breakthroughs, but the reason it is not happening more is

1 because in the competent host, these breakthroughs are
2 virtually all susceptible.
3 I guess one final point is how would you expect a
4 creme--and I think it is another jump to say that a creme
5 applied to the lip is actually ever seeing a latent site at
6 all; in other words, with systemic therapy in HIV, you can
7 imagine that the drug is getting there, but why would there
8 be an effect on latent infection, because it is hard for me
9 to imagine how there is any drug exposure at that level.
10 DR. BRASS: So is part of your argument that in
11 fact, intrinsically, virulence and resistance are inversely
12 related?
13 DR. SACKS: We know they are as an average. There
14 are examples of exceptions--like Don Coen's letter said and
15 I think Earl quite well spoke to--everybody admits that
16 there are resistant isolates. The argument that was made by
17 Burroughs Wellcome with acyclovir was wrong, that when TK-
18 negative, it is nonvirulent, don't worry about it. It was
19 an exaggeration of the truth. Clyde Crumpacker spoke to
20 that at those meetings.
21 We all agree now that there are exceptions, that
22 there is TK-negative virus that can be virulent; there are
23 mixed populations that can complement, so even if it is 99
24 percent TK-negative and still resistant, it still can have
25 enough TK to be virulent. But actually, that represents a

1 very small number of isolates. Some of them are now being
2 worked through in animal models, and it does look like you
3 can have true TK-negative virulent--there are probably
4 virulence factors that can outweigh the loss of TK.
5 All I am saying is that clinically, the ones that
6 become resistant and recur with resistant virus absent drug
7 pressure so far have all reverted to wild-type if you leave
8 the patient off drug. That's just what we have observed.
9 It is not a lot of patients; it is a very few patients.
10 DR. MARKS: In terms of Dr. Coen, his information
11 wasp ut into the mathematical model in terms of the worst
12 case, doomsday scenario planning. We approached him and had
13 Dr. Lipsitch work with him. Since he is not here to address
14 that, in the transition to going to surveillance--in terms
15 of mathematical modeling and transmission, just to let you
16 know that those factors are in there.
17 Mark, do you want to talk about transmission and
18 that model?
19 DR. LIPSITCH: Could I have my third slide,
20 please, in the mathematical modeling set?
21 [Slide.]
22 DR. LIPSITCH: Earlier, I spoke only about the
23 question of acquired resistance because that was the
24 question that came up. Originally, the mathematical
25 modeling was done strictly on the question of transmission

1 of resistance, and it was in fact a peer review or a sort of
2 informal peer review by Dr. Coen which suggested that we
3 should look at the question of acquired resistance.
4 What we have done in the modeling is to consider
5 these two questions separately--first the transmission and
6 then the accumulation of individuals who acquire resistance
7 during treatment. So if I could speak briefly to the
8 transmission question--next slide, please.
9 [Slide.]
10 DR. LIPSITCH: The model that we used to look at
11 transmission of resistance had several key assumptions and
12 parameters. The basic assumption is that new infection is
13 proportional to the current prevalence of either sensitive
14 or resistant virus. It is a transmissible disease, and the
15 number of people out there carrying the virus is
16 proportional to how likely one is to acquire it.
17 We assumed that up to 30 percent of cold sore
18 sufferers use topical penciclovir, as I described earlier.
19 We assumed that topical penciclovir reduces transmission of
20 sensitive herpes type 1. It is clear from the studies that
21 it reduces shedding; it is not yet documented whether it
22 reduces transmission. But if there is going to be any
23 selection for antiviral resistance, it will be through this
24 mechanism--if there will be any selection in transmission of
25 antiviral resistance, it will be through this mechanism of

1 reducing the transmission of sensitive virus.

2 We assume that individuals are infectious when

3 they have cold sores, and also possibly when they are

4 asymptomatic; so we consider both that they are or that they

5 are not transmitting when they are asymptomatic.

6 We assume that there may or may not be a fitness

7 cost or a transmissibility cost to resistant virus. So at

8 worst, they are just as transmissible as sensitive virus,

9 and as a maximum fitness cost at best from the perspective

10 of resistance, they are 50 percent less transmissible.

11 We assume for the transmission modeling that there

12 is no acquired resistance--we considered that separately

13 later, or earlier today.

14 And finally, we assumed to begin with that there

15 is total or partial immunity to super-infection, secondary

16 infection with HSV-1, once you have HSV-1.

17 Next slide, please.

18 [Slide.]

19 DR. LIPSITCH: The basic model is a compartmental

20 model, very similar in spirit to Sally Blower's model.

21 People are born susceptible and then become infected either

22 with drug-sensitive or drug-resistant virus, and once they

23 are infected, they may experience cold sores, and those cold

24 sores may be treated or untreated. Treatment, as I said

25 earlier, we assume reduces the duration and possibly the

1 intensity of shedding of sensitive virus, and thereby may
2 select for the transmission of resistance. It is a
3 competitive process between transmission of resistant virus
4 and sensitive virus, so inhibiting sensitive virus
5 transmission is the way that you could favor resistant virus
6 transmission.
7 Next slide.
8 [Slide.]
9 DR. LIPSITCH: That was a very simple model, and
10 one of the considerations in developing it was are we making
11 such oversimplifications that we are somehow missing ways in
12 which resistance could come faster. And I won't go into
13 detail in describing this diagram of our more complex model,
14 but I will just say that we included three factors which in
15 fact increased the rate at which resistance spread in the
16 model. We allowed the possibility of dual infection--from
17 sensitive, you can become infected with resistant and
18 sensitive, and vice versa. We included an age structure in
19 the model, and we included an immunocompromised class.
20 Next slide, please.
21 [Slide.]
22 DR. LIPSITCH: And actually, just in the interest
23 of time, I'll go to the next slide.
24 [Slide.]
25 DR. LIPSITCH: So what we got out of that--we said

1 let's look at the worst case assumptions that seem plausibly
2 consistent with existing data, erring always on the side of
3 parameter estimates that would make resistance come faster,
4 so we assumed high levels of treatment, 30 percent. We
5 assumed that treatment cuts the duration of shedding of
6 sensitive virus by 25 percent, which is in the literature;
7 and we assumed that it cuts the amount of transmission
8 during shedding by 90 percent, which is not in the
9 literature, but is just magnifying the selective force,
10 because there is no data on that.
11 We assumed that resistant HSV-1 has no difference
12 in transmissibility from sensitive, and we assumed that
13 asymptomatic shedding makes no contribution, so all of the
14 possible transmission is selected by treatment.
15 And when you consider transmission of resistance
16 alone, ignoring acquired resistance, we find that even with
17 these worst-case assumptions, you have very, very slow
18 arrival of resistance, very similar to what Sally Blower's
19 model found for HSV-2, that in particular, you get about 70
20 years to go from 0.3 percent to 1.3 percent. And because of
21 the way the spread happens, the numbers in the
22 immunocompromised are very similar.
23 So that is the transmission of resistance side of
24 the story that complements the acquired resistance earlier.
25 DR. BRASS: Thank you.

1 DR. WOOLSON: Could I ask a follow-up question?

2 DR. BRASS: Piease.

3 DR. WOOLSON: I had a question about this model

4 and also the other model. I was wondering how robust these

5 models are to these model assumptions you are making. You

6 keep referring to these are "worst case" assumptions, for

7 example, this 30 percent of the cold sores treated, but if

8 it were 45 percent, for example, in the previous model you

9 gave us earlier this morning you had a range of 60 to 200

10 years--what happens to that 60 to 200 years in that case?

11 DR. LIPSITCH: Right . In the previous model, it

12 is essentially linear in all those factors; so if you went

13 from 30 to 40 percent, then 60 years would go to 45 years.

14 In this part of the model, in the transmission

15 model, it is not linear, and in fact, I would have to run it

16 with these assumptions in particular, but the rate of

17 increase is limited not primarily by the amount of treatment

18 but rather by the natural rate of turnover of infections. I

19 think one of the letters earlier alluded to the fact that

20 there is a large reservoir of virus from the old days, and

21 that reservoir effect continues--infections turn over slowly

22 with the life span of the human host, not with the life span

23 of the virus. So that is the limiting factor--so it would

24 still be many decades, but I would have to check and see

25 exactly.

DR. WOOLSON: And one relatively small question. What confidence do you put in that statement there, the conclusion? We usually think of things in terms of 95 to 99 percent confidence. Is this stocastic at all, or is this a completely deterministic model?

DR. LIPSITCH: It is a deterministic model, and it is hard to put confidence intervals on a particular number, because the parameters each have a range, and while there are ways of combining those ranges, I am not sure they are particularly better than looking at scenarios.

If you run the model, as I said, with even worse assumptions that are not consistent with what we expect to be true, you can reduce it to maybe 50 years, but you are not reducing it an order of magnitude; you are not reducing it very noticeably.

DR. YOGEV: Can I ask a follow-up question here?

DR. BRASS: There is one thing I wanted to ask in follow-up, and then 1'11 come back to you.

In regard to Dr. Woolson's question, then, because of that large reservoir effect that you alluded to, is it not also then a characteristic of the model that two things happen once you reach a certain threshold of resistance--one, it accelerates quickly as the reservoir is depleted, so that it may take 60 years to get to one percent, but then very many fewer years to get to 10 percent; and second, that

1 because the reservoir is now re-established with resistant
2 strains, stopping the use of the antiviral doesn't rapidly
3 decrease the prevalence, and in fact it continues to
4 increase for a while.
5 Are those two fair statements from the model?
6 DR. LIPSITCH: Let me address the first one first.
7 The spread of resistance in this part of the model, in the
8 transmission model, is roughly speaking an exponential
9 process. It is a little faster than exponential at the
10 beginning because of a cohort effect, and then it flattens
11 out to an exponential process. So this is a roughly four-
12 fold rise in 70 years, from 0.3 percent to 1.3 percent--and
13 that is assuming, by the way, that all of the people, all of
14 the 0.3 percent, have transmissible resistance, which is
15 almost certainly--
16 DR. BRASS: Yes, I understand.
17 DR. LIPSITCH: --but if you assume that, that is a
18 four-fold increase. The rate for another four-fold increase
19 would actually be a little bit slower than 70 years because
20 of this cohort effect. So to get to 5 percent, roughly,
21 would take about 100 more years; so 170 years to go from
22 where we are now to 5 percent.
23 So the reservoir continues, because most people
24 who are exposed to virus are exposed to sensitive virus for
25 many years to come.

1 DR. BRASS: Dr. Yogev?

2 DR. YOGEV: A couple of clarifications, if you
3 don't mind. I read the original paper in JAMA, and it
4 sounds like you make an assumption of 25 percent less
5 shedding, while the data are three and three days in those
6 groups, and if you look at those who start a little later
7 with treatment, there is no difference at all.

8 Secondly, where did you get the assumption that
9 transmission will be reduced by 90 days? The utmost of
10 shedding is within 48 hours. It takes three days to get rid
11 of it. I didn't see any data anyplace that in a number of
12 viruses, the lesions are less.

13 Dr. LIPSITCH: Right. let me address those
14 separately. The first one, you are right, there is no
15 reduction if you just compare the medians, I think it is--it
16 is three and three. What we were using was the hazard
17 ratio, which is more sensitive and actually more applicable
18 to the rates that are considered in this model, and that is
19 where the 25 percent came from.

20 In reference to your second question--and it is
21 actually relevant to the first also--if there is no effect
22 on shedding, then this whole part of the model just becomes-
23 -there is no selection, and nothing happens in the
24 transmission of resistance part of the model.

25 So you are right, there is no data saying 90

1 percent reduction in shedding. That was, in our mind, a
2 vast overestimation of how much there could be. If you take
3 that away, then the rate at which the resistance comes in is
4 much slower.
5 DR. BRASS: Dr. Marks?
6 DR. MARKS: That last point is incredibly
7 important in terms of taking an optimistic view in terms of
8 how much impact we have on acyclovir-sensitive shedding.
9 Taking an optimistic view on that actually makes the model
10 more pessimistic. So if you take away that pressure, the
11 years go much further out. So if you don't believe this has
12 an impact on acyclovir-sensitive or penciclovir shedding,
13 the times are huge.
14 DR. BRASS: Dr. Lipsky?
15 DR. LIPSKY: Yes. In the over 20 countries,
16 including UK, Australia and Germany, in which there is OTC
17 availability for herpes labialis--and I presume most of that
18 is for acyclovir; I don't know--has that model been applied
19 even to what has happened in those countries, or is there
20 not enough data on resistance or whatever? Do we know what
21 is going on, because that seems to be a pretty big exposure,
22 whether it is acyclovir or whatever, to 20 countries.
23 DR. MARKS: Twenty countries have--
24 DR. LIPSKY: It says topical acyclovir was
25 approved in 1991 as an OTC treatment for recurrent herpes

1 labialis in New Zealand, and is now available OTC in over 20
2 countries. So it looks like there are a few million people
3 exposed. Is that model for what is going on out there, or
4 do we not know the resistance, or are we just totally
5 ignorant of what is going on in those 20 countries?
6 DR. LIPSITCH: We haven't formally attempted to
7 put in parameters for each country. The best I can say to
8 that is that in the British context of five years of OTC
9 acyclovir, there hasn't been a detectable increase, and
10 that's what the model predicts. Now, whether that means
11 that it is thousands of years off or tens of years off, we
12 can't say, but it means at least tens of years off, as I
13 described.
14 DR. LIPSKY: Are those 20 countries the European
15 Union, or what are they? Is it possible to have a good
16 handle on that?
17 DR. LIPSITCH: The countries in which we ran our
18 trials, the pivotal trials from which we obtained isolates
19 from, were throughout Europe, Singapore, Canada and the
20 U.S., so we have a broad variety of isolates that we put
21 together that the data was presented earlier by Dr. Levin in
22 terms of where that information comes from.
23 And in terms of these surveillance programs, they
24 pop up in various places around the world.
25 DR. LIPSKY: Do you know in those 20 countries

1 what proportion of people who have the illness are self-
2 treating?
3 DR. MARKS: Actually, I do not know that, unless
4 John Copeland from our International and Worldwide Market
5 Group can respond to that.
6 DR. COPELAND: Yes. I did actually mention that
7 this morning. What we found in Europe was anywhere from 3,
8 5, to a maximum of 11 percent of all sufferers have access
9 to a topical treatment for their cold sores. Following the
10 availability of OTC via the creme, that figure did rise, and
11 the highest figure got up to about 50 percent. However,
12 that was after many years, a number of years, in the case of
13 Europe going back to about 1992.
14 The situation, however, is that that figure is
15 actually slowing down. That is the situation that we found.
16 In regard to the 20 countries, 17 of them are in
17 Europe and 3 are in the old, sort of commonwealth countries
18 like South Africa, Australia and New Zealand. So that is
19 the situation as we have it today.
20 DR. LIPSKY: Yes, I think you did mention that.
21 Thank you.
22 DR. BRASS: Yes?
23 DR. KODA-KIMBLE: I wonder if the sponsor or any
24 virologist could respond to the comment by Dr. Oxman, which
25 bothers me quite a bit, and that is: "Most isolates of HSV

1 obtained today reflect shedding of virus by latently
2 infected persons whose infections predated and/or were
3 independent of any use of acyclovir. Given the vast
4 reservoir of latent acyclovir-sensitive HSV, it will be some
5 time before the emergence of resistant virus is reflected in
6 the overall population of HIV isolates."
7 Is that a probably true statement?
8 DR. MARKS: First off, I want to talk about the
9 fact that when we put together the panel where we brought in
10 the group that Dr. Whitley spoke about earlier, we talked
11 about having people who were for the switch, and we had
12 people who were against the switch. We invited Dr. Oxman to
13 come and present his views in that discussion so they could
14 be taken into account by that panel, so many of the
15 arguments outlined in his letter were discussed openly and
16 privately by the group as well, to put that into
17 perspective.
18 Probably Dr. Leary or Dr. Levin can answer that
19 from the virology point of view.
20 DR. LEVIN: I think Dr. Oxman is only partly
21 right, that we're talking mostly about genital isolates that
22 we have studied in the recent past, and most people who are
23 coming in to have genital isolates cultured in an STD
24 clinical setting are fairly young people, and they have
25 acquired their herpes simplex genital infections many years

1 after the nucleoside analogs were out in the community, and
2 we should start to see an effect of increasing prevalent if
3 in fact that were happening.
4 That would be my answer to Dr. Oxman. That is
5 also the reason to continue looking.
6 DR. BRASS: Any other comments on that particular
7 point.
8 DR. LEVIN: Dr. Sacks wants to comment.
9 DR. SACKS: I agree with what Myron said, but I
10 would just point out that to a certain extent what Michael
11 is saying is the same as what the mathematical modelers are
12 saying. If I understand correctly, there definitely is a
13 huge latent pool of sensitive virus that is going to remain
14 the predominant pool of a period of years, and that does
15 influence how long it will take. That is one reason why the
16 mathematical model shows it is going to take 70 years. So
17 there are both sides.
18 DR. BRASS: Are there other questions?
19 Please.
20 DR. YOGEV: I wonder, if that assumption is true
21 that it is only what happens in nature, and there is no
22 pressure, why are we saying 10 times 4 to 20 times 4 is the
23 new compromise?
24 DR. MARKS: I didn't understand the question.
25 DR. BRASS: I think it is related to the selection

1 pressure. What is the basis for the 10-fold higher
2 incidence of resistance in the immunocompromised patient as
3 compared to the immunocompetent.
4 Dr. SACKS: The immunocompromised host is a quite
5 different situation, first of all because--it's just like
6 HIV--the amount of virus that is present is substantially
7 increased by several logs. Second, the continuous pressure
8 of viral shedding never goes away so there is no immune
9 response to clear the virus, which in a competent host
10 happens within a couple days. And thirdly, the drug
11 pressure which is usually systemic continues unabated in the
12 presence of high viral replication in the absence of an
13 immune response. So there is drug pressure causing
14 resistance.
15 I think it is not clear that there was an
16 immunocompromised host shedding rate, that 5 percent
17 predating acyclovir. I'm not sure--there is. Okay. So
18 maybe I should let Earl talk about that. But I think the
19 point is that there is a mutation rate already present, so
20 if you look at virus as a heterogeneous pool, there is a
21 small amount of that pool that is already resistant, and how
22 much was present statistically prior to the advent of
23 acyclovir--
24 DR. KERN: Five percent in one study.
25 DR. SACKS: You are saying 5 percent, so in one

1 study, it's 5 percent. It seems to me that drug pressure
2 must play a role. However, clinically, it seems relevant to
3 me whether the data show what the data show, that the more
4 immunocompromised you are and on drug pressure, you are at
5 risk of resistance, but the data don't show a change.
6 DR. BRASS: Yes?
7 DR. OLIVO: I think it's important to point out
8 that that data that was presented about there being no
9 change in the percentage or the prevalence of resistance
10 pre- and post-acyclovir therapy was not fully comparable in
11 that different methods were used. And the issue that Dr.
12 Sacks talked about in terms of the methodology to find sub-
13 populations was not applied. So the data has to be taken
14 with some grain of salt. There is some possibility--I don't
15 know how great--that the prevalence is higher, and we just
16 haven't been able to detect it.
17 DR. SACKS: I'll just say one thing about
18 methodology. The literature for plaque reductions goes back
19 an awfully long time, so really, there hasn't been much
20 change in the last 20 or 30 years in terms of what the
21 general principle of plaque reduction is. There are a lot
22 of variabilities, and penciclovir is really a funny drug in
23 testing, because it is very cell-dependent when you test it.
24 When we try to depend on number, they don't mean a lot; but
25 on the other hand, what does mean a lot is that when you see

1 true acyclovir resistance that is clinically relevant in the
2 compromised host, usually, in a TK-negative situation, which
3 is 99 percent of them, the numbers are huge; they just
4 become flat-out neutral to the drug.
5 So even though there are still--we cannot have a
6 standardized method for penciclovir testing because there
7 aren't enough resistance isolates to say what is clinically
8 relevant and what is not. We only have one paper that
9 looked at that with acyclovir, clinically, and showed 2
10 micromem [ph.] per ml using a certain assay. But with
11 penciclovir, there haven't been enough resistance to really
12 characterize; that's going to have to come with time or not,
13 depending on how many resistant isolates we see.
14 But I think the FDA has expressed a lot of concern
15 about quantum and characterization and standardization, and
16 that is something the Task Force is working toward, and
17 NCCOS has a subcommittee that I am on that is trying for the
18 first time to come up with standardized assays, so that is
19 happening. The problem is that I think clinically, those
20 things don't matter, because clinically, the really
21 resistant ones just shoot way off the scale, and they are
22 usually quite obvious and stand out from the others. So I
23 don't think we should get too bogged down in absolute
24 numbers, and whether it is one micron per ml in one assay or
25 0.1 in another is probably not important.

1 DR. OLIVO: I agree. I guess you would be saying
2 that you would disagree with Don Coen's comment that some of
3 the isolates that have less, that are not resistant to high
4 levels but rather to moderate levels would be clinically
5 relevant?
6 DR. SACKS: Yes. There are in-between resistance
7 isolates that are fairly rare. The polymerase mutants, for
8 example, which we describe with acyclovir show there is a
9 medium-range resistance, where instead of 20 microns per ml,
10 they go up to 2 or 3 microns per ml, or 4 or 5 microns per
11 ml. So there is a little more subtle change.
12 There is also one in 1,000 isolates that fits that
13 characterization. Don's characterization is absolutely
14 accurate. I think we all agree that there is resistance,
15 that resistance can be virulent, even though it is most
16 often not, and this has been observed for years, and I think
17 all the experts in the field agree that that can happen.
18 The question is, is there any change in how it is happening,
19 or does that really even fit or is it relevant to the issues
20 that I talked about in terms of whether topical in a
21 competent host applies.
22 I think the Don Coen letter is factual, but it is
23 very specific around the virology of resistance and not
24 necessarily about the global picture of using penciclovir in
25 a population, from my own point of view.

1 DR. BRASS: As a non-virologist, this is one of
2 the things that concerns me about the methodology. If we
3 could have your original Slide 48 from this morning's
4 presentation.
5 [Slide.]
6 DR. BRASS: this shows the influence of acyclovir-
7 resistant HSV in immunocompetent patients. You show data
8 over time, from both the dye uptake and the plaque reduction
9 methodology along the top there, and superficially, it looks
10 to me like the dye uptake gives a 10-fold higher resistance
11 than the plaque reduction, superficially.
12 [Slide.]
13 DR. BRASS: Then, when you go to the next slide,
14 we see over time--we change from the dye uptake to the
15 plaque reduction, and the plaque reduction at 6 percent is
16 now being compared to the dye uptake at 6 percent as a "no
17 change" where, based on the previous slide, a 6 percent
18 plaque reductio would be a 60 percent dye uptake difference,
19 if there is really a fixed, 10-fold difference in the two
20 methodologies.
21 DR. LEVIN: Yes, we actually talked about that,
22 and no one knows the exact answer because experiments
23 haven't been run side-by-side--that's the problem. But I
24 think the sense that we have is that the background and the
25 nonspecific dye uptake is so high in the dye uptake test,

1 that to see a positive--there is quite a smearing between a
2 positive and the high background, whereas there is not that
3 smearing in the isolates from the immunocompetent patient.
4 When you get to the immunocompromised patients,
5 when you see them high, they are truly high.
6 DR. BRASS: The question is whether in Slide 49,
7 the next slide, that 6 percent in dye uptake is really
8 comparable to the 6 percent plaque reduction to give us
9 confidence that there has not been a dramatic increase.
10 DR. LEVIN; Yes, I understand the question, and I
11 think Dr. Leary is going to say it better than I did--
12 although I agreed with his explanation.
13 DR. LEARY: I don't know if I can say this
14 accurately, and actually, there may be other people here who
15 can tell us about the dye reduction uptake discussions that
16 went on between the groups that did dye uptake and plaque
17 reduction earlier.
18 What I think is happening is the dye reduction
19 assay, or dye uptake assay has a very low dynamic range, and
20 I think the cut-off is set very, very close to being too low
21 and that you are getting a lot of false-positive resistance
22 isolates that are perking right along the cut-off point.
23 When you go over to the immunocompromised state,
24 where you actually have a bunch of resistant isolates, those
25 guys get way up top, at the top of the dynamic range, and

1 they are truly resistant. This is not an issue where you
2 are seeing in the first immunocompetent patients a 10-fold
3 increase in sensitivity. You are cutting the tops off the
4 mountains.
5 DR. BRASS: So you would say the 5.8 percent has a
6 narrower confidence interval based on the test methodology
7 as compared to the 2 percent in the previous slide?
8 DR. LEARY: Yes, I think that's accurate, and I
9 don't know if there is somebody here who may be able to
10 discuss--
11 DR. KERN: The uptake assay is less sensitive.
12 DR. BRASS: Are there other questions? Please.
13 DR. FEINBERG: I d on't know if this is a question
14 so much as a comment. I guess I have some concerns about a
15 number of the presentations earlier today that made things
16 seem maybe a little bit more black and white than they
17 really are.
18 For example, let's posit that resistance rates, at
19 least in immunocompetent patients, are really very low.
20 That may be true of a population basis; however, when an
21 individual has a resistant infection, it is really quite a
22 devastating medical situation, because the alternatives are
23 all toxic, parenteral drugs, and the individuals, of course,
24 who are most likely to have resistance are people who have
25 damaged biology to begin with, so you are talking about

1 chronic toxic parenteral therapy. So the rates may be low,
2 but for a given individual, the occurrence of it is
3 devastating.
4 I think the other thing I somehow came away with,
5 and maybe I was just confused, but it seemed to me that at
6 least one or more presenters made it seem as if the
7 population of virus in an individual is also somehow some
8 sort of all-or-none phenomenon, and if patients with HIV
9 infection are any kind of model--and they are probably a
10 reasonable model for immunocompromised individuals--then
11 mixed population of virus is actually the norm and not the
12 exception. In other words, people have an episode of
13 herpes, it cultures resistant, they get treated, they
14 relapse, it is sensitive, they get treated, they relapse, it
15 is resistant--and on and on.
16 So I think it is evident to me, at least in my
17 experience, that you can certainly have established in a
18 single individual mixed populations of virus with regard to
19 susceptibility. And I don't know who it was who exactly
20 spoke to this, but somehow I was left with the impression
21 from the presentations that people sort of felt like if you
22 are already infected with sensitive virus, nothing further
23 is going to happen, and I was certainly concerned about
24 that.
25 DR. MARKS: I don't know if I gave you that

1 impression or not. I think that what we are talking about
2 with topical application is that the reservoir within the
3 ganglionic site is unlikely to be infected since there is no
4 systemic level associated with penciclovir.
5 So in the immunocompetent host, when they have
6 recurrences, they are sensitive, the drug pressure is local,
7 and the reactivations would be expected and anticipated to
8 be sensitive virus.
9 In the immunocompromised individual, again, no
10 systemic concentrations with topical application, therefore,
11 the reactivation may well be unaffected by that.
12 So in terms of the management of HIV-infected
13 patients with parenteral formulations and isolations of
14 subsequent strains being resistant or sensitive, I
15 understand exactly what you are talking about. The
16 impression we are trying to give you is with topical
17 application, how that differs.
18 Earl, did you want to comment?
19 DR. KERN: I just want to make a quick comment. I
20 think some of us believe that all virus populations are
21 mixed. Encountering a pure population in nature, I believe,
22 is not feasible.
23 It is well-documented that patients can go back
24 and forth from resistant to sensitive, and one of the
25 patient we have in the Task Force study that I mentioned

1 earlier was resistant nine months ago. Three subsequent
2 isolates, three subsequent episodes now, have all been
3 sensitive.
4 So clearly, these go back and forth. I think
5 Steve Sacks had a beautiful explanation, that that part of
6 the population that is resistant by and large is probably
7 less virulent and less able to survive in the environment,
8 where the sensitive, wild-type outgrow and therefore become
9 sensitive again instead of resistance.
10 DR. BRASS: Dr. El-Sadr?
11 DR. EL-SADR: This is not exactly on resistance,
12 but I am just curious since this drug has been approved as a
13 prescription drug for a while now, and you certainly have
14 had, I assume, the opportunity to advertise to consumers
15 directly, like with a lot of other medications that we see
16 advertisements for. In spite of that opportunity, somehow--
17 I don't know if you have done that or not; that's the number
18 one question. Number two, there is a decrease in the use of
19 the topical agents in this country. Have you attempted to
20 reach out to consumers directly, since a lot of our patients
21 now are walking in, saying, "I saw this on TV," or "I saw
22 this in a magazine. Will this work for me, or not?"
23 DR. MARKS: To answer your question, George
24 Quesnelle from our Marketing Group can speak specifically to
25 what activities we have engaged in.

1 MR. QUESNELLE: We have tested direct-to-consumer
2 advertising with denavir because it is such a consumer-
3 driven kind of condition, and we tested it for six months.
4 It was a typical kind of test that we do of advertising in
5 cities that were matched in terms of population
6 demographics. What we found was that we got a less than
7 two-tenths of one percent increase in the number of
8 prescriptions for the product.
9 The issue is it is very difficult to get people to
10 change their behavior and go to physicians with a primary
11 complaint of cold sores when they are so used to taking OTC
12 treatment and their treatment into their own hands. So that
13 basically, it was a very disappointing result.
14 DR. BRASS: What I'd like to do at this point is
15 go around the table and ask each panel member if he or she
16 has some statement relevant to the charge from the FDA that
17 they would like to summarize their feelings about the
18 resistance issue.
19 I'll start with Dr. Olivo.
20 DR. OLIVO: Well, I come from the bias that
21 increased use is going to lead to increased resistance. I
22 think we have to accept that as a likely scenario, because
23 we have enough information from other viral and bacterial
24 systems.
25 But I do agree with a lot of the statements that

1 have been made that suggest that specifically with this
2 issue, the likelihood of an increase in resistance is right
3 now low, but we have to say that we really don't know what
4 it is, and the data won't allow us to draw a conclusion.
5 I think it is true that the fact that denavir will
6 be used for a short period of time, topically, is going to
7 greatly reduce the likelihood of promoting resistance. I
8 think it is true that HSV does have a low level of mutation
9 rate relative to RNA viruses like HIV. I think it is true
10 that penciclovir and acyclovir-resistance viruses, whether
11 they are TK-deficient or altered, have a reduced virulence,
12 although there is a defined possibility that some isolates
13 that will evolve will be less or more pathogenic than we are
14 led to believe. It is also true, and it has been mentioned
15 several times, that immunocompetent patients clear resistant
16 virus very effectively, and that reduces the likely
17 opportunity for selection of resistance in the
18 immunocompetent patients.
19 But as I say, having said all that, I think we
20 have to be honest and say we really don't know what the
21 selected pressure that widespread use of penciclovir
22 topically will confer, and the big concern is that if we are
23 wrong, and it turns out that these assumptions are incorrect
24 and that there is an increase, this is going to be a large
25 boat that we will not be able to turn quickly; that the

1 prevalence of latent virus in the latent population is going
2 to be something we are going to have to be stuck with for a
3 long period of time. So we are talking about our children's
4 children here in terms of the prevalence of resistant virus.
5 Twenty to thirty years from now, if it goes up to 5 percent
6 in the immunocompetent patient, it's going to be a long time
7 before that is reduced, regardless of what we do.
8 Those are my concerns as it relates to resistance.
9 I have other issues as it relates to the merits of the
10 switch, so to speak--
11 DR. BRASS: We'll get to those.
12 DR. OLIVO: --but we'll get to those; okay.
13 DR. BRASS: Dr. El-Sadr, you asked to make your
14 comments now, because you have to leave.
15 DR. EL-SADR: Yes, unfortunately, I have to leave.
16 I will not give my summary comments, but I echo
17 the comments that were just made. I am concerned, as with
18 any other infectious disease, about the implications of
19 widespread use of an agent especially when we don't have a
20 lot of classes to use for fighting various viral infections.
21 So I am very concerned about the potential sequelae maybe
22 20, 30, 40 or 50 years from now, although I am somewhat
23 reassured by some of the resistance data that have been
24 shown earlier today.
25 I think this drug does have a value and should be

1 used appropriately in patients who suffer from herpes
2 labialis. I do think there is an educational effort that
3 needs to be made, and I am rather surprised by the effort
4 that was made to try to reach consumers directly and that
5 that did not have much of a response. That makes me think
6 about the whole wisdom of the switch from prescription to
7 over-the-counter.
8 I think that what needs to happen is an
9 educational effort to reach patients who suffer from these
10 conditions to seek help and that there is a specific
11 treatment for it rather than the symptomatic treatments that
12 probably do not work, as was indicated earlier today.
13 DR. BRASS: Thank you.
14 Dr. Reeves?
15 DR. REEVES: I would essentially agree with what
16 was said. I would agree with the comments that resistance
17 right now is probably low. I think the modeling would
18 indicate that we really don't know how quickly this may or
19 may not increase.
20 From my perspective or CDC's perspective, I think
21 the problem is how to put in appropriate surveillance. It
22 was very easy to do surveillance for HSV-2 resistance,
23 because essentially, you have a population which you can
24 easily sample at STD clinics, and the theoretical questions
25 of how to sample the population for HSV-1 resistance, or

1 even what population to sample, are quite different.

2 I think one of the things that I have been

3 particularly impressed with is the interest, in at least the

4 two companies that we have worked with, Glaxo and

5 SmithKline, to seek advice from CDC, to seek advice and put

6 together a really excellent task force. I have seen a very

7 proactive attempt to get at these issues and try to begin

8 the thought process of how to monitor it. It is already

9 over-the-counter in many places. These issues are going to

10 happen, and I think our concern or the public health concern

11 is how we can in fact determine what the problem really is

12 now and how to sample appropriate populations and to get at

13 that. And I think that a lot of the answer is partnerships

14 between the companies, academia, and the government to try

15 to put some of these kinds of things into place.

16 DR. BRASS: Thank you.

17 Dr. Laughlin?

18 DR. LAUGHLIN: I essentially agree with virtually

19 all the previous speakers. I think that if the product is

20 used correctly, as the labeling indicates, the risk for a

21 lot of development of resistance is very low. However, I

22 think it is very clear that we really don't have data in

23 this area and that even though post-marketing studies are

24 not supposed to be linked to approval, I think it would

25 certainly make many of us feel very much more comfortable if

1 the company, as it seems to have already, makes a firm
2 commitment to conduct the studies.
3 I think one of the difficulties will be--Dr. Kern
4 mentioned earlier that he would prefer to do studies in the
5 immunocompromised patient. This over-the-counter indication
6 is not for that patient, and I do not know if the oral
7 formulation of famciclovir would fill that need.
8 There may be an additional need to look at
9 immunocompetent people who are frequent recurs and their
10 contacts.
11 DR. BRASS: Thank you.
12 Dr. Woolson?
13 DR. WOOLSON: I too agree with much of what has
14 been said.
15 DR. BRASS: We can just put ditto marks around the
16 comments.
17 DR. WOOLSON: Right. But I am trying to separate
18 what is low versus what is unknown here, and I guess I would
19 agree with everyone that the estimate is that the rate of
20 production of resistant mutations is low.
21 I think the range of uncertainty is very, very
22 wide on that--and I'm still sorting that out in my mind--
23 particularly if we take a look at particular groups, the
24 immunocompromised and the STD populations. And as I look
25 more broadly at the whole issue of risk-benefit, it is that

1 uncertainty that is causing me some questions as I think
2 through this.
3 DR. BRASS: Thank you.
4 Dr. Yogev?
5 DR. YOGEV: Just to make a different tone, I
6 disagree with my previous colleagues--no, no.
7 [Laughter.]
8 DR. YOGEV: I have a major issue with having a drug
9 moving into OTC when a certain population which is a
10 majority who probably get these cold sores are not
11 investigated, and we don't know what is going on. I am
12 referring to the very elderly, children, and the
13 immunocompromised, since the disease is different in those
14 populations, and to make an assumption from what we know
15 from a competent, 40-year-old, highly educated female--it is
16 wrong to let this bull leave the barn and hope it will not
17 step over this population.
18 DR. BRASS: Again, we are focusing now on
19 resistance. We'll come back to the switch issue itself.
20 DR. YOGEV: Also--and maybe this should be later--
21 but on the education issue, I think we are overemphasizing
22 it. To give an example, education for HIV, STD and so
23 forth, to put that it will work, and because somebody puts
24 on the label "x", it is a major issue that I still have not
25 resolved that it will do the right thing.

1 DR. BRASS: Dr. Diaz?

2 DR. DIAZ: I'll add my "ditto"; I basically agree
3 with what most of my colleagues have already said. In
4 particular, I am a little bit disappointed, in a sense, that
5 we don't have any data at all that has been presented about
6 resistance in individuals who are frequent recurs and who
7 have been frequent users of this drug over-the-counter in
8 other countries. It seems like the opportunity has been
9 there to get some of that information, and yet we don't have
10 that information.

11 Likewise, in particular, my comments about
12 resistance go hand-in-hand with concerns about misuse. The
13 modeling that has been presented, to my knowledge and
14 understanding at this point, doesn't have any criteria for
15 modeling that deals with issues about increased resistance
16 secondary to perhaps misuse and selective pressure in
17 individuals for lower drug concentrations and lesions
18 leading to perhaps higher levels of virus that are then
19 under a selective pressure to create more resistant virus.
20 And if there is modeling to that effect, I would like to
21 know, but I would think it would be somewhat almost
22 impossible to come up with criteria to even look at that
23 issue at this point.

24 Finally, one might argue--it may not be correct,
25 but one might argue--that the reason that drug resistance

1 hasn't changed perceivably that much, quote-unquote, over
2 the years with increasing use of antivirals, particularly
3 for herpes infections, is that they have been fairly well-
4 controlled in the sense that, despite increased usage, there
5 has been less potential for misuse of the drugs in terms of
6 issues about using them for shorter periods of time, lower
7 concentrations, one day here, one day there, et cetera. So
8 I am a little bit skeptical about any kind of predictions
9 for the future in terms of what the resistance might be at a
10 later date and time without some of that baseline
11 information.
12 Likewise, I log the concerns for the individual
13 and the issues about surveillance on a population base. It
14 will take a long time to see changes on a population base,
15 and yet to the individual who develops or has resistant
16 virus, it is a major, major issue for that individual in
17 particular.
18 DR. BRASS: Thank you.
19 Dr. Feinberg?
20 DR. FEINBERG: I do think the previous speakers
21 have very much summarized, and very nicely, too, what the
22 main issues are, so I am not going to go over that again.
23 I just want to actually underscore two things that
24 were also said by other members. One, Dr. El-Sadr made the
25 point that the current drugs we have for herpes infections

1 all have the same target, the same mechanism, and that
2 certainly complicates the issue of resistance even if
3 resistance is uncommon. I think Dr. Woolson also made a
4 good point about investigation into people who do have
5 frequent recurrences and are the people who are going to be
6 the primary users of a preparation like this a larger
7 percent of the time.
8 A number of times during the day, people made
9 reference, by the way, to decreased shedding; yet, under
10 treatment, it is intuitive and it makes some logical sense--
11 but I could never find any information in this packet that
12 showed me those data, so that is an aside, and maybe it
13 would be nice if someone could point out where that is.
14 DR. BRASS: Dr. Masur?
15 DR. MASUR: We all seem to agree that we have
16 little evidence about resistance and that we need more
17 evidence. I guess I'm troubled by two things. We have a
18 potential for harm that is hard to measure when we are
19 working with a mathematical model because we don't have hard
20 data. We then have to balance that risk of resistance with
21 two other factors. One is our confidence that this drug
22 will be used appropriately by consumers. When we have dealt
23 with drugs in the past that have potential adverse effects,
24 we have been skeptical about our ability to educate health
25 care professionals about the appropriate use of drugs. We

1 know that many health care professionals do not use drugs
2 appropriately in terms of their indications or their
3 toxicities.
4 So I guess I am far more skeptical than anyone
5 else here that this drug will be used appropriately for
6 herpes labialis either in terms of the number of
7 applications needed or the number of days needed. I am
8 skeptical that it will be avoided by patients with risk
9 factors like immunosuppression or that it will not be used
10 by people with herpes genitalis given the fact that it will
11 be available, and it is clearly a nuisance to have to go to
12 a health care professional and get care that is expensive
13 and inconvenient.
14 I am also concerned that while the issue of
15 efficacy is not on the table because the FDA has already
16 ruled on that, the evidence that this provides a substantial
17 clinical benefit is extraordinarily limited, and I think
18 there are probably those who are not so convinced that a
19 half-day or one-day or two-day difference is enough of a
20 benefit to outweigh the potentials for risk that aren't
21 measured.
22 So I guess I am much more troubled by the lack of
23 information about resistance as a risk compared to a benefit
24 that I am not sure is really substantial. And I would
25 suspect that if many of the experts who were up here

1 speaking were asked do they use topical drugs, the answer
2 would be that most of them do not--they use oral drugs. And
3 I think that says something about the benefit from this kind
4 of preparation.
5 DR. BRASS: Dr. Lipsky?
6 DR. LIPSKY: There has been much discussion on the
7 potential implications, as the question states, of the use
8 of denavir on the prevalence of resistance to HSV. The
9 answer to that question or that discussion is, of course,
10 that we don't know. But then it comes down to numbers. It
11 appears that all the mathematical models make the assumption
12 that increased use of the drug will lead to increased
13 resistance. With that, what is the risk of that, or what is
14 the harm that is done? Well, how you use numbers is
15 interesting. In one way, you can just show "p" values that
16 are very statistically significant and not the actual
17 difference that they are measuring. That is one use of
18 numbers. Another use is to magnify small effects, so that
19 for instance, if the resistance is 0.3 now and goes to 1.5
20 in 20 years, and we are going for efficacy, and we turn that
21 into efficacy, we would announce it as a five-fold increase
22 in efficacy because we have done this. Such things are done
23 with some clinical trials.
24 But the reality may be that in 20 years, there may
25 be "a five-fold increase" in resistance. What does that

1 mean to a patient who most needs it, someone who is
2 immunosuppressed--the bone marrow transplant--in whom you
3 wish to use acyclovir if, say, we still need to use it 20
4 years hence? What would that mean?
5 Well, that's an interesting and problematic
6 situation. If that were the unlucky individual who may be
7 the one out of 50 or so who might be infected or have
8 problems with a resistant organism, would that individual be
9 happy with the fact that maybe that was due to selective
10 pressure because there was large-scale use of trying to
11 decrease by half a day or a day a cold sore?
12 Those are problematic issues which I don't think
13 there are clear answers for but which I think we must take
14 into consideration.
15 DR. BRASS: Thank you.
16 DR. McGrath?
17 DR. McGRATH: My only point to add would be to
18 really emphasize the issue that you just raised in terms of
19 the risk-benefit, because I find that throughout the day, at
20 different times, we have been asked, based on different
21 amounts of information or different interpretations of
22 existing information, to think about making a decision as to
23 what is the comfortable risk we are willing to take in terms
24 of increased resistance over time--how much time is a
25 comfortable margin, how much surveillance is a comfortable

1 amount--and I think that we need to continue to weigh that
2 against the issue of the benefit. And I was really pleased
3 that you brought that up.
4 DR. BRASS: Dr. McKinley-Grant?
5 DR. McKINLEY-GRANT: I guess I have to be a
6 "ditto" of everything that has been said. One of the
7 concerns that I have is the transmission of resistant
8 organisms, but on the other hand--because 20 years from now,
9 I don't want to be known as part of this panel that approved
10 this drug that caused resistance--but on the other hand,
11 there is a group of people who really need this medication.
12 But I am also very concerned that I'm not sure how well it
13 works--and I know we aren't supposed to bring up the
14 efficacy--but part of me says, well, we may not have to
15 worry about resistance because if there is only a 17 percent
16 refill rate of the prescription, then it is not a product, I
17 don't think, that is being highly used and effective.
18 But just as a precedent, I think the concerns that
19 my colleagues have raised about the resistance are crucial.
20 DR. BRASS: We're going to try to cut their
21 marketing director a break here and quit picking on him.
22 Dr. Koda-Kimble?
23 DR. KODA-KIMBLE: I have nothing to add. I think
24 the issue as far as resistance goes relates to the public
25 health risk over a 30-, 40-, 60-year period versus the

1 potential benefit to individuals. I worry about that.

2 DR. BRASS: Ms. Hamilton?

3 MS. HAMILTON: Well, as the consumer

4 representative, I find that I am approaching this discussion

5 perhaps from a more polemic than scientific viewpoint, and I

6 am happy to defer to the science community here and listen

7 with respect to all the comments that you have had.

8 My concern is whether or not this discussion

9 belongs in our discussion of an OTC switch and whether or

10 not this isn't a discussion that belongs in the big picture,

11 not separate from the prescription utilization of this

12 product. When we are on the Nonprescription Drug Advisory

13 Committee often having these discussions, I think we try to

14 stay very focused on efficacy and safety as the primary

15 considerations. It seems to me there is no question about

16 the effectiveness and the safety of the product, so I worry

17 when we begin to introduce new criteria--and this happens on

18 a product-by-product basis sometimes--into the way we make

19 this decision.

20 I listened to Dr. Katz set out for us some of the

21 bases for making the safety determinations, and we talk

22 about drug interactions and toxicity, neither of which is an

23 issue in this discussion. I just want to raise the concern

24 that perhaps this discussion, which I respect, on ultimate

25 drug resistance belongs in a bigger picture and is not

1 relevant to the decision we have to make today about an OTC
2 switch.
3 DR. BRASS: Thank you.
4 Dr. Blewitt?
5 DR. BLEWITT: Thank you.
6 I agree that resistance is the extraordinary issue
7 as it pertains to this product, and it was the key issue
8 when I attended the meeting four years ago on acyclovir.
9 I must say that there are certain things that are
10 different in this case, and I am impressed with the efforts
11 that the sponsor has made to put together a comprehensive
12 resistance surveillance program. They have confronted the
13 issue up front, and they intend to look at this issue in
14 many ways.
15 Now, you cannot know what is going to happen
16 unless it does happen, so the idea of conducting
17 surveillance programs is not realistic--unless the product
18 is actually OTC. So there is kind of a chicken-and-egg
19 effect here, too.
20 I think a lot turns on viral versus bacterial
21 resistance, and the extent to which you can extrapolate from
22 all of the discussions on bacterial resistance to viral
23 resistance. And certainly I think the sponsor has made a
24 convincing argument that these differ and that you can look
25 at viral resistance in very different ways than we

1 traditionally look at bacterial resistance. I think that
2 that is a most important point.
3 Then, of course, the question is how much
4 surveillance is enough, and that turns to the question of if
5 you can't really do this, are these products totally out of
6 consideration. That then takes you to the fact that
7 somehow, there is an important gap in terms of access to
8 this drug. Either patients go to physicians to get a
9 prescription for it, or they don't get it at all. And
10 because of the nature of the illness, it is not something
11 that they are going to readily go to the physician for.
12 So the fact is, then, that they won't take it at
13 all, and one then begins to philosophize as to what are the
14 expectations when a product is approved--is it hoped, then,
15 that the consumption will be so low that it really won't
16 create any problems with regard to increased resistance, or
17 is the key to approving these drugs to allow access for as
18 many people who have the disease process as can be done?
19 Those are my comments and also questions that I
20 would throw out to the committee.
21 DR. BRASS: Thank you.
22 Dr. Krenzelok?
23 DR. KRENZELOK: Thank you.
24 There appears to be a tremendous gap here, from a
25 doomsday mentality to some very strong evidence, and we seen

1 to exist in a more evidence-based society these days. But I
2 would not purport to have a great deal of expertise in
3 infectious disease, so I won't pontificate on that point any
4 longer.
5 I think that what is really important here is a
6 program of very aggressive education, and surveillance that
7 is very aggressive as well in the sentinel populations, sa
8 was discussed this morning. I think that if we do that, we
9 can go a long way toward making sure we don't hit the
10 doomsday end of it, and we can maintain the other end of the
11 evidence base.
12 DR. BRASS: Dr. Gilliam?
13 DR. GILLIAM: As I work primarily with bone marrow
14 transplant patients where I have seen resistance to
15 acyclovir and some of the other antiviral medications, my
16 big concern regarding this topic was the development of
17 resistance. And I was reassured somewhat by Dr. Sacks and
18 some of the other Task Force members that this does not seem
19 to be as much of an issue with the topical ointments. So I
20 was glad to hear this. And I agree with the previous two
21 committee members and their comments.
22 DR. BRASS: Thank you.
23 Dr. Sachs?
24 DR. SACHS: I agree with a lot of what has been
25 said, but from a general perspective, I guess we are trying

1 to balance here the potential benefit against the risk.
2 Potential benefit as presented is modest, and if you look at
3 the renewal data, if 83 percent of people do not renew
4 prescriptions, was that because it was no longer necessary,
5 there was no recurrence? Was it because it didn't work, or
6 they didn't perceive a big benefit in actual use trials?
7 We are balancing it against the possible risk of
8 resistance, which is either low or unknown, and to me, that
9 is actually a big question. I think that if we were dealing
10 with something that was very clearly effective, then maybe
11 the low risk or an unknown risk would be worth taking. But
12 I think we have heard a lot of information that the risk-
13 benefit may not be there, while I will grant the safety data
14 is there, and the potential for misuse is probably low--
15 although it was shown there, too, it is never going to be
16 zero, in this case, it would be very low.
17 DR. BRASS: Thank you.
18 Dr. Neill?
19 DR. NEILL: Yes, a switch from prescription to OTC
20 would result in an increased prevalence of resistance.
21 DR. BRASS: Please, Dr. Reeves?
22 DR. REEVES: I just realized something as I was
23 listening to this, particularly Ms. Hamilton. I think it is
24 clear, technically, to me from what has been presented that
25 putting penciclovir over-the-counter is not what is going to

1 turn the tide to herpes virus resistance.

2 We have a tremendous problem now with antibiotic

3 resistance, and that occurred when they were all being

4 prescribed by physicians. There is a large number of

5 thymidine analogs which are prescribed by physicians. The

6 resistance that we measured with the Task Force was probably

7 due to prescription drug. It seems to me that, again

8 particularly with the commitment of the company and the Task

9 Force and CDC, that there is in fact a unique opportunity to

10 put into place surveillance for resistance to most of the

11 thymidine analogs as part of the licensure of one product

12 going over-the-counter, and in point of fact, a larger

13 question can be addressed in the question of this one drug--

14 I mean, the amounts of drug that are going to be sold, the

15 modeling based on one drug--that single drug is not going to

16 do it, but a bigger question exists which in point of fact

17 the company and others of us are interested in approaching

18 as part of the licensure potentially of this.

19 DR. BRASS: I think that that is an extremely

20 important point, because again, as a non-virologist

21 listening tot his, if this 180 kilograms leads to resistance

22 in 20 years, what is the other 100,000 kilograms doing? So

23 there is sort of a non-reality about that kind of

24 extrapolation in the context of the overall market.

25 Dr. Katz, Dr. Jolson, have we adequately discussed

1 that particular issue to meet your objective?

2 DR. JOLSON: Yes. Thank you.

3 DR. BRASS: Great.

4 DR. OLIVO: Can I make one comment about the

5 surveillance?

6 DR. BRASS: We are going to get into surveillance

7 in more detail.

8 DR. OLIVO: We are. Okay.

9 DR. BRASS: The second specific question that ew

10 have been asked to consider is: Based on the data presented

11 and the benefits/risks associated with the use of the

12 product, do you recommend the approval of denavir for OTC

13 use for the treatment of herpes labialis in immunocompetent

14 adults?

15 I would like to begin this discussion by asking

16 the sponsor two questions. The first has to do with OTC and

17 the recognition of what I recognize is already a monographed

18 indication, and specifically, whether the phrase "cold

19 sores" is universally understood by all ethnic groups to

20 identify the indication. In Hispanic groups, in Chinese

21 American groups, is this the term that is used to describe

22 these lesions?

23 DR. MARKS: The terms "cold sores" and "fever

24 blisters" are very commonly recognized.

25 George, do you know about sub-populations of

1 Chinese Americans, et cetera?

2 MR. QUESNELLE: We studied the label in low-

3 literacy, but not necessarily in specific ethnic groups, so

4 we don't have information on people of other languages. We

5 do know that "cold sore" is the most common phrase used to

6 describe them. Second to that, although much lower, is

7 "fever blister."

8 DR. BRASS: Again, it's not just a question of

9 language; it's an issue of culture. And again, there is a

10 variety of common disease entities which are described by

11 phraseologies in the immigrant Chinese community in English

12 that we would have no idea what they were talking about

13 unless we had an English translator to interpret the ethnic

14 context of this. So I am concerned about the

15 generalizability of the indication in the current U.S.

16 culture. I don't know what it was when the original

17 monograph was generated.

18 MR. QUESNELLE: What we can look at it who was

19 involved in the use trial, and also, in a major study that

20 we did with the Gallup organization, which was a study

21 trying to determine who are the cold sore sufferers out

22 there--this is random, digit-dialing-type technique, so it

23 is a projectable sample of the U.S.--you see up there the

24 numbers of people we got from various ethnic groups in terms

25 of being cold sore sufferers.

1 [Slide.]

2 MR. QUESNELLE: A specific answer to your

3 question, is there something in the Chinese culture, I don't

4 have an answer to that.

5 DR. BRASS: The second question goes to the issue

6 of efficacy in the decision tree. In several places in your

7 description in the printed material, you suggested that in

8 the two pivotal trials that in fact the integrative efficacy

9 of the product may have been minimized by using a vehicle

10 control and that the vehicle itself may be contributing to

11 the efficacy. And you cited that your primary data to that

12 that the vehicle alone had substantially shorter durations

13 of lesions and pain than a variety of historical controls.

14 The only true placebo control is the sun blister

15 study, which had much smaller numbers, and it wasn't clear

16 how it would extrapolate to the more general indication.

17 Do you have any thoughts or comments that would

18 help us have some perspective on that?

19 DR. MARKS: That was the exact reason for why we

20 put together the pilot study that is outlined in the

21 briefing document looking at sun-induced cold sores to try

22 to tease out that difference.

23 In the JAMA article, where Dr. Spruance put

24 together the average healing time of an untreated cold sore,

25 taking data from the placebo arms of oral trials, it was

1 roughly in the neighborhood of seven to eight days. In our
2 denavir program, the vehicle group was five days. I believe
3 we have information on that.
4 [Slide.]
5 DR. MARKS: So if we take the whole disease as a
6 spectrum--this is the same slide that Dr. Spruance went
7 through; this is the one that walks through the stages--and
8 if we take the next slide, where we just blank that out and
9 call this "no treatment"--this is the underpinnings for your
10 question and also the reason for doing the study--if you
11 take that, and you superimpose these, it is not identical
12 because it is taken from historical data, and I'll give you
13 that caveat, which you understand already.
14 Next slide.
15 [Slide.]
16 DR. MARKS: If we put the vehicle alone over that,
17 we see that there is a discrepancy between what the
18 historical data would be and that of the vehicle; and if ew
19 put denavir back in, it would be between the vehicle and the
20 no treatment group in terms of having increased efficacy
21 above and beyond that.
22 So this is a formulation that is specifically
23 designed to treat cold sores, and whether or not it has an
24 impact on that, we put it together into the program that we
25 outlined earlier.

1 [Slide.]

2 DR. MARKS: So when we look at that data in sun-
3 induced cold sores, we see roughly a day to a day-and-a-half
4 impact on the disease.

5 Now, I am not going to try to tell you whether or
6 not the vehicle has an impact, but there is a discrepancy
7 between what we can deliver with denavir versus the vehicle,
8 and what we can deliver with denavir versus a true placebo
9 such as water. Now, that's a vehicle effect, that's one
10 explanation. The other is that denavir indeed does deliver
11 more efficacy than what was demonstrated in the trials.
12 There are a lot of reasons for that, and I'll take just
13 another second.

14 In terms of oral formulations and people talking
15 about how much efficacy with oral formulations, I will
16 remind everybody--and I am sure you already know--that there
17 are no oral formulations approved for the treatment of this
18 disease, and if you look at the literature on those studies
19 done multiple years ago, a decade or more ago, and you look
20 at the trial design and the rigor of the analysis with which
21 we went through in terms of FDA approval, which we are very
22 happy we did because it shows convincingly that it does
23 work, but comparing that analysis set with decade-old
24 information, with one-sided statistics, efficacy-evaluable
25 populations and very small numbers of individuals, and then

1 saying that oral formulations have lots of efficacy, and
2 topical formulations don't have efficacy, we take issue
3 with.
4 We believe this is the first compound--the first
5 compound, oral, topical, whatever--that has been
6 convincingly demonstrated to speed the healing of cold
7 sores. And we did that to the nth degree in terms of our
8 working with the FDA over making sure that our data was
9 rigorous and extensive.
10 Seven hundred individuals whom we didn't know
11 whether or not they used the drug, or we knew that they
12 didn't use the drug but had a cold sore, were included in
13 the analyses in a variety of ways, and when you load in data
14 that is either neutral or durations of zero, you can make
15 the impact just by the methodology look smaller than it is.
16 That was pointed out in the JAMA article in terms of looking
17 at how data is, so if you look at some regulatory packages
18 or in the JAMA article, it is 0.7 to one day; if you look at
19 it in our treated versus untreated trial, you go up to one
20 to one-and-a-half days.
21 The information on genital herpes and what impact
22 we have on acute management, regardless of which compound it
23 is, it is very similar in terms of its efficacy and its
24 nature.
25 So we believe denavir is truly effective.

1 DR. BRASS: Dr. Masur?

2 DR. MASUR: I am impressed with the rigor of the
3 studies and the fact that the studies do in fact show a
4 difference. I guess what I'm struggling with, if you could
5 put that last slide up, is as to whether the public would
6 really be benefitted from having this available, and that
7 has to do with the magnitude of the effect.

8 One thing I want to understand on this is how you
9 define "relative clinical severity," since that is the
10 parameter you are measuring, rather than crusting, viral
11 shedding, et cetera.

12 DR. MARKS: I'll be happy just in a second, and
13 I'll ask Ron to get ready to show you the treated versus
14 untreated in terms of the benefit by the investigator and
15 the patient. But let me respond to this.

16 [Slide.]

17 DR. MARKS: This is from Dr. Spruance's article
18 written probably a decade ago. The relative clinical
19 severity scale is his assessment or understanding of how
20 patients believe is. So this is not our measure; this is us
21 laying over what existed in the literature.

22 So in terms of that, all this says in terms of
23 relative clinical severity is that vesicles are painful,
24 noticeable and problematic; ulcers are, too. They are much
25 more so than the prodrome period, which is the first little

1 square, and they are more so than the hard crust stage, and
2 by the time you get to losing the hard crust, where there is
3 just residual erythema and dry flaking, it is a very
4 relative clinical severity, a very small amount.
5 Ron, could you put up the slide?
6 [Slide.]
7 DR. MARKS: Now, here is what happens in these
8 studies when we have two groups--to remind you, this is the
9 blinded study where we used purified water versus denavir.
10 If we go on down the list--show me the efficacy at the end--
11 in terms of asking people about clinical severities as well
12 as the investigator on the clinical side.
13 [Slide.]
14 DR. MARKS: So time to lesion healing, just to
15 remind you, was impacted, statistically significant--200
16 patients--this is even larger than the historical literature
17 studies on oral products.
18 [Slide.]
19 DR. MARKS: If you look at duration to hard crust,
20 lesion size, investigator shows time to healing, lesion size
21 and duration of pain are statistically significant. If you
22 ask the patient, "Are your lesions smaller?" the answer is
23 yes. If you measure them--on the diagram before this--the
24 answer is yes, all statistically significant. How
25 noticeable was it; the amount of scab or crust you have; the

1 swelling; the cracking; the overall severity of your
2 disease, how do you rate it compared to the other untreated
3 groups--meaningful, in our opinion, clinical, statistically
4 significant impact.
5 Do we have the perception of effectiveness?
6 [Slide.]
7 DR. MARKS: Yes. So if we ask the investigator,
8 just tell me about whether or not you believe that one group
9 or the other--this is blinded; they don't know--highly
10 effective--you see that penciclovir is rated higher.
11 Effective--penciclovir is rated higher. And when you get to
12 moderately or modestly or ineffective, then placebo begins
13 to outweigh it.
14 So in terms of effective or highly effective, the
15 investigator tells us that denavir works.
16 Next slide, please.
17 [Slide.]
18 DR. MARKS: If we ask the subject does it work,
19 again, denavir, highly effective or effective outweighing
20 placebo.
21 So whether we do scientific rigor, "p" values,
22 medians, means, hazard ratios, Kaplan-Meier plots, it works.
23 If we ask people does this improve your disease and the
24 management of your illness, in clinical trials, the answer
25 is yes, and in our one-on-one interviews and focus groups,

1 when we ask how do you like our product, does it work, the
2 answer is yes.
3 DR. BRASS: Dr. Koda-Kimble, did you want to make
4 a comment? I know you have to leave momentarily.
5 DR. KODA-KIMBLE: Yes, I'm sorry I have to leave,
6 and I just wanted to place my vote.
7 DR. BRASS: Why don't you give it to us--don't
8 state it.
9 DR. KODA-KIMBLE: Okay.
10 DR. BRASS: Dr. Neill?
11 DR. NEILL: I am curious to know whether there is
12 any clinical or marketing data to suggest that OTC
13 availability of denavir in any of the markets in which it is
14 currently available OTC results in initiation of treatment
15 earlier, at an earlier stage of disease than we otherwise
16 see with prescription availability.
17 DR. MARKS: Again, it is our perception that that
18 is the case--
19 DR. NEILL: Is there any data?
20 DR. MARKS: We don't have hard data on how did you
21 use it, but if you look at the prescription environment, 90
22 percent wait until they have a cold sore; and if you ask
23 people when they are applying it--and actually, in the
24 actual use trial, we actually do have data, do we not? It
25 does increase, and I am trying not to give you the wrong

1 number--

2 DR. NEILL: Let me--I want to be real specific.

3 Is there data to suggest that initiation of treatment occurs

4 at an earlier stage of disease--not do patients use it more,

5 but do patients use it and initiate treatment at an earlier

6 stage of disease?

7 DR. BRASS: Earlier than what?

8 DR. NEILL: Earlier than in a prescription

9 environment.

10 DR. BRASS: So the answer is--the hypothesis has

11 been stated that patients will actually use it earlier.

12 DR. MARKS: Specific information on denavir,

13 because of the limited number of markets where it is

14 available without prescription, we do not have data on that.

15 Appendix 9, page 195. Maybe I am wrong.

16 If you could just give us a second, we can project

17 that slide as well.

18 [Slide.]

19 DR. MARKS: I think I'll have to speak to it,

20 since I can't read it. Okay, great. Has everybody found

21 that.

22 If we look at the stage of the cold sore lesion--

23 this is from the actual use trial where we put it into the

24 pharmacies--if you look at the number of cold sores at

25 enrollment in the people who responded to it, this chart

1 goes through the information that is available on that. I'm
2 not sure the audience can see that from the back, but the
3 panel certainly can in their journals.
4 So if you look at cold sores at enrollment versus
5 no cold sore at enrollment and when they respond to that,
6 you can see that no cold sore at enrollment, which is what
7 you are talking about--people coming in, and do they use it
8 in this environment--"when I could feel a cold sore coming
9 on, but before it was visible" is 43 percent, and the cold
10 sore enrollment was 22 percent.
11 DR. FEINBERG: Although that doesn't really
12 address--
13 DR. MARKS: It approximates, or hopefully helps,
14 but I agree.
15 DR. NEILL: It's useful information, but it
16 doesn't answer the question, so I'll take that as a "No, we
17 don't have any data."
18 DR. MARKS: So I'll stick with my first answer.
19 DR. FEINBERG: And your question is really only
20 relevant the first time a patient needs to seek medical
21 assistance to get the prescription. Once the prescription
22 is sitting in your medicine cabinet, you can self-medicate
23 at will.
24 DR. NEILL: Well, that's an entirely different
25 question. It is a different question. The shelf-life

1 appears to be on the order of a year to a year and a half,
2 so the unasked question that is implied by that is given a
3 prescription environment, what would it take in terms of
4 switching to OTC to get patients to use it more quickly, and
5 that is an issue that hasn't been discussed. We have talked
6 about education, et cetera.
7 DR. BRASS: unless there are some extremely
8 pressing clarifications or questions, what I'd like to do
9 now because of the hour and the departure of too many
10 members is do the formal voting process on the question.
11 Is there anything critical?
12 DR. MARKS: I would just like to take 30 seconds
13 to talk about commitment, because a lot of people have asked
14 about commitment. The FDA does have the ability to withdraw
15 the drug from the market, no question about it. The reason
16 we prospectively put together our program in terms of
17 surveillance and worked with CDC and with ISAR and our
18 colleagues in industry is the fact that we are committed to
19 this issue and this area.
20 In terms of Phase 4 commitments, we take those
21 very seriously. We put together the group in order to do
22 that. We are committed to this area and to doing that.
23 And if the decision of the independent groups
24 involving the CDC, ISAR, NIH, FDA, whoever ultimately gets
25 on that panel, is that this drug should be removed from the

1 market, there is no question in our minds that we will
2 remove the drug from the market.
3 DR. BRASS: Thank you.
4 Again, the issue we are going to be voting on is
5 "Based on the data presented and the benefits/risks
6 associated with the use of the product, do you recommend the
7 approval of denavir for OTC use for the treatment of herpes
8 labialis in immunocompetent adults?"
9 I would just, in terms of my own comments,
10 emphasize some of the points that were made in terms of the
11 unknown characteristics of the risks, but lots of reason to
12 believe that the resistance issue has to be low. And as I
13 indicated previously, if the 20-year estimate is real, then
14 all the rest of the use is going to mean that by the time we
15 leave this room, there is going to be such an incidence of
16 resistance from the use of the other products on the market
17 since we have been here, it is just a huge-magnitude issue.
18 And I think that the lowness of that low number, as has been
19 pointed out, while uncertain, I think there is reason to
20 believe it is very low, and the issue of whether
21 surveillance is adequate to protect the public from it is a
22 separate question.
23 I will remind you that the only people who are
24 eligible to vote are in fact people who are authorized panel
25 members or SGE consultants. That is Drs. Feinberg, Diaz,

1 El-Sadr, Masur, Lipsky, myself, McGrath, McKinley-Grant,
2 Koda-Kimble, Ms. Hamilton, and Drs. Woolson and Yogev as SGE
3 consultants. So if you are not on that list, please do not
4 vote, or you will cause confusion on the ballots.
5 All those in favor, or who would vote yes, "Based
6 on the data presented and the benefits/risks associated with
7 the use of the product, do you recommend the approval of
8 denavir for OTC use for the treatment of herpes labialis in
9 immunocompetent adults?" please raise your hand for yes.
10 [A show of hands.]
11 DR. BRASS: All those who are opposed to the
12 proposal, please raise your hand.
13 [A show of hands.]
14 DR. BRASS: In addition, we have votes from Drs.
15 Woolson and El-Sadr, who are also against; both are against.
16 All those abstaining? I hope there aren't any,
17 because we have 12 votes.
18 [No response.]
19 DR. BRASS: So the vote is 5 yes, 7 no.
20 Dr. Jolson?
21 DR. JOLSON: If we could just clarify the yes
22 votes in terms of how many there were.
23 DR. BRASS: If you voted yes, please raise your
24 hand again.
25 [A show of hands.]

1 DR. BRASS: It is quite along committee lines,
2 actually.
3 Dr. Katz, with that close a vote, are you
4 comfortable? Do you want us to discuss the issues more?
5 How would you like us to proceed?
6 DR. KATZ: Actually, I would like, if possible, to
7 go back and answer the rest of the questions.
8 DR. BRASS: So even the "yes" questions?
9 DR. KATZ: Well, actually, there is a "no"
10 question for the "no", and there is a "yes" question for the
11 "yes".
12 DR. BRASS: I see.
13 DR. KATZ: So if we could go back, since it looks
14 like the majority of the panelists said "no", if we could
15 address the second half of the question--"If 'no', what
16 additional studies do you recommend?"
17 DR. BRASS: Okay. For those of you who voted
18 "no"--I guess if you voted "yes" and you still want to
19 answer, you can still make a comment--based on your "no"
20 vote, what additional studies do you recommend or would be
21 required to change your view of this?
22 Dr. Yogev?
23 DR. YOGEV: I think the way the question was posed
24 caused me to say "no" because you take it out of the context
25 of the population, just what it does in immunocompetent.

1 And I think the study which would help me to make a decision
2 and change is the populations which are going to use it when
3 it would be OTC, the immunocompromised children, the
4 elderly. And to address the issue which you raised so
5 nicely, that is, the cultural differences, I am not at all
6 convinced that education will pick up all the problems which
7 we have. So I think we need to see more studies into the
8 minorities. This is almost a discriminatory study. It was
9 done in Caucasian, 90 percent, only adult immunocompetent,
10 and as a whole, we have a lot in our population who have
11 more of these disease that we need to see in those types of
12 studies.
13 DR. BRASS: So the issue of doing studies in
14 immunocompromised or in children where the product is not
15 indicated would be to answer what questions?
16 DR. YOGEV: Yes, because today, when you have
17 somebody still [inaudible], hopefully, the physician with
18 prescription will make sure those populations will be
19 treated. OTC, you don't have that. And you need to make
20 sure that we have some safety net so that it will not affect
21 negatively those types of populations.
22 DR. BRASS: So you'd want a safety study in those
23 populations?
24 DR. YOGEV: Safety and efficacy would be part of
25 it, too, because--the same issue which we raised, the

1 resistance, I think the problem is in those populations.
2 They have the disease longer. In pediatric, for example,
3 they have the disease much longer than in adults. I am not
4 aware if anybody checked the amount of virus. I personally
5 believe that if you have 10 to the 6th versus 10 to the 8th,
6 maybe the resistance is already there which you are
7 selecting out, which might be much more seen if we take
8 enough immunocompromised patients.
9 So yes, for safety, to approve it for
10 immunocompetent, because I know, and everybody in the field
11 knows, that there are many other populations who supposedly
12 do not use it are going to use it and suffer from it.
13 DR. BRASS: Are there other "no" votes?
14 Dr. Lipsky?
15 DR. LIPSKY: Well, I don't think it is really so
16 much w hat another study will involve. It is an issue of
17 what we do in 1998 with anti-infectives when we look at the
18 abyss of the post-antibiotic or anti-infective era or that
19 possibility, and what is the heritage that we leave to our
20 children, our grandchildren and our great-grandchildren, and
21 what is the responsibility of a regulatory agency to deal
22 with that problem, whether it be in OTC, whether it be an
23 agricultural product, whether it be physicians or health
24 care practitioners prescribing the drug.
25 So I don't really think in terms of what is the

1 study that is going to put it over.

2 DR. BRASS: So you would extend--if I might

3 paraphrase--that it would be very difficult for you to

4 envision any antimicrobial over-the-counter?

5 DR. LIPSKY: In this day and age, when we are

6 becoming more aware of resistance and whether the

7 mathematical model predicts it is going to be 0.3 going to

8 1.0, or 1.5, or whatever, I think there is a great

9 responsibility that society must place on us that we should

10 feel for the absolute wisest use of these agents, which we

11 have only had for a couple of generations, to make certain

12 we have them for future generations.

13 DR. BRASS: I think that's exactly the point of

14 this question in that this is an opportunity to help define

15 what studies would be required to provide the degree of

16 information or certainty or safety that would allow you to

17 vote comfortably for an antimicrobial in the future.

18 DR. LIPSKY: But it is also an issue which we face

19 all the time in our medical centers and in our hospitals, of

20 what are the best indications to be using anti-infectives;

21 where should be best be using them and how--even for the

22 approved indications, even for the approved indication of

23 this agent.

24 DR. BRASS: Dr. Masur?

25 DR. MASUR: I would agree with what Jim Lipsky has

1 said, but I would add that the kinds of surveillance studies
2 in general populations or specific populations that are
3 necessary have been well-outlined. The problem to me is
4 that with any microbial agent, as Jim suggested, there is a
5 potential resistance, and the question is what is the
6 benefit.
7 I would agree with Dr. Marks that the company has
8 clearly demonstrated the benefit of this agent. So the
9 question is how much of a benefit do you have to have to
10 warrant any risk. If this were a drug which prevented life-
11 threatening illness, it wouldn't be an issue. If this were
12 a drug which could abort herpes labialis, and if you took
13 it, you didn't get the disease at all, it would be a much
14 different risk-benefit ratio, and then we would be in a real
15 philosophical quandary about the long-term societal
16 interests versus the interests of an individual.
17 I think we unfortunately simply have an honest
18 difference of opinion that I simply can't see any reason to
19 approve this given the very limited clinical benefit that I
20 interpret--and I realize that other reasonable people may
21 disagree as to whether or not that benefit warrants the
22 wider availability of this drug.
23 DR. BRASS: Dr. McGrath?
24 DR. McGRATH: Thank you. I am a "yes" person, but
25 I just wanted to comment that I found this extremely

1 difficult in terms of some of the decisions for all the
2 reasons that have been mentioned, but also the tendency to
3 sometimes go backwards, as I think you mentioned, Kathleen,
4 and look at issues as they apply to perhaps the approval of
5 the original prescription drug.
6 I found myself thinking at different times that
7 one of the issues is that as an individual, I am lucky
8 enough to make a decision in terms of what the clinical
9 benefit or the meaningfulness of the drug for me would be,
10 for example, in that I'd have access to a physician and a
11 prescription. But I find myself asking should that same
12 right to choose be denied to someone else because they don't
13 have equivalent access to a physician. And I think I find
14 myself being led more toward wanting to deal with the bigger
15 issue but in essence feeling that the real issue is whether
16 what is available now should be available to a wider segment
17 of the population with appropriate surveillance education
18 and moving forward in a different way than we have done
19 before.
20 DR. BRASS: Ms. Hamilton?
21 MS. HAMILTON: I also found this to be a tough
22 one. It is interesting to me that the risk-benefit analysis
23 in this instance changes with the increases use of the
24 product, and that is interesting to me--so that when the
25 risks and benefits were evaluated for prescription use, I

1 assume some level of usage was probably predicted or
2 anticipated, and so of necessity in looking at OTC
3 utilization, that necessarily changes the way you make that
4 evaluation.
5 I would hope that one thing that might come from
6 this discussion, however, is the acknowledgement that the
7 issue that has been raised here is no less significant for
8 prescription utilization of this product than it would be
9 for over-the-counter, and I would hope the members of this
10 committee and the FDA would develop appropriate studies in
11 order to evaluate what the maximum use of this product ought
12 to be, even if it continues to be a prescription-only
13 product. I think that prescribing doctors are entitled to
14 that information and that they now hold the entire mantle of
15 responsibility for ensuring that we don't overutilize the
16 product. It is important that we give them the tools with
17 which to make those decisions.
18 DR. BRASS: Dr. Diaz?
19 DR. DIAZ: I think when you ask the question about
20 what further studies would need to be done, obviously, we
21 always want more data, so obviously, more susceptibility
22 data or resistance data in end-users would be among that
23 group. But there have been many experts here today who have
24 presented their best guess and ideas based on what data does
25 exist as to what the risks are in the future, and some have

1 been very positive in terms of not having much concern that
2 resistance will be rampant and go out of control versus
3 others who were a little more conservative in that regard.
4 But nonetheless, the resistance issue aside, the
5 kinds of issues that I was struggling with this drug in
6 particular had to do with some of the criteria that were
7 mentioned for over-the-counter switch. And even if I put
8 concerns about resistance aside and side with those of less
9 concern, there are a couple of issues for over-the-counter
10 switch that I didn't think were particularly addressed--in
11 particular that the product has a low capacity for misuse or
12 abuse. And I wasn't clear in my mind that the sponsor had
13 presented enough data to satisfy that concern in my mind
14 that there was a low potential for misuse because of issues
15 that had been previously stated about elderly, looking at
16 people of other cultures, patients who have sexually-
17 transmitted diseases, and in particular patients who are
18 immunocompromised in terms of their ability to read the
19 label and actually be able to use this drug and use it
20 appropriately.
21 In particular, too, with the study that was done,
22 it was a little provocative to me in looking at the self-
23 responses versus the hypothetical responses and wondering if
24 the dichotomy in that had to do with the fact that patients
25 were asked "would you use it", and perhaps their answer

1 being, Yes, I would use it, I fully understand the label, I
2 recognize that I am not a person who should use it, and yet,
3 yes, I would--but when asked hypothetically should this
4 person in this category use it, they responded that no, they
5 shouldn't use it, appropriately.
6 So my concerns in particular about the over-the-
7 counter switch are along the lines of the potential for
8 misuse and abuse. And also along the lines of can it be
9 labelled effectively, I think probably it could be labelled
10 effectively at some point, but I am not sure that the label
11 that currently exists would be effective for promoting less
12 misuse in the community.
13 And finally, issues about is it effective, would
14 this drug be effective marketed for consumers in particular
15 as opposed to patients. When we hear data that says that
16 most consumers use it three or four times a day, I'm not
17 sure that the therapeutic benefit that we found in the
18 controlled trials using it more frequently would actually
19 exist if it were marketed for the consumer and used perhaps
20 less frequently, so the benefit may actually not be there
21 for the consumer per se.
22 DR. BRASS: Dr. Feinberg?
23 DR. FEINBERG: Dr. Diaz and I chatted sub rosa
24 here, and I concur with her read of the criteria as they ere
25 presented to us by the FDA for what is involved in the OTC

1 switch. In addition to agreeing with what she just said, I
2 want to address two things.
3 One, the specifics of the question what other
4 studies should be done, in my mind, I think some of the
5 questions we need to have answered are these: Do treated
6 patients shed through therapy, and if so, how often does
7 that happen? Do they wind up shedding resistant virus from
8 this local skin site, and can resistant virus be acquired de
9 novo by their close contacts? I think Dr. Laughlin kind of
10 outlined the patient population in whom this could be best
11 studied are people with frequent recurrences, and then you
12 look at their close sero-negative contacts and see what
13 would happen. That is actually not a small study; that
14 would be an immense piece of work.
15 But along the lines of what are much more general
16 charges before you come to sit on this committee, which is
17 first do no harm, then I think you need to be armed with
18 some information to make those decisions. And actually, the
19 least comment I wanted to make has to do with the
20 philosophical issues at hand, which Ms. Hamilton brought up.
21 But the fact is that always in medicine, you are confronted
22 with decisions or a tension between the rights or the well-
23 being of a given individual who sits before you and what is
24 good for the overall welfare of society.
25 I think it is interesting that the vote was very

1 much along committee lines, and I think a lot of people who
2 are not dealing with infectious disease every day think
3 about is that in all other drugs and applications, there are
4 only two elements to the situation--I understand that you
5 are frustrated about it, but let me just say that there are
6 two elements to the situation. One is the person, the
7 consumer, the patient--that is a biologic system--and then a
8 drug, and what happens--is it safe, does it work.
9 When you deal with infectious diseases, you change
10 the dynamics of this interaction entirely, because now you
11 have two living organisms which behave independently--not
12 entirely independently, but that can respond in different
13 ways. And the three-way dynamic between drug, pathogen and
14 human being is a lot more complex, both biologically and
15 statistically, than most people want to deal with at the
16 surface.
17 So I understand you are frustrated because it
18 seemed like the rest of us were throwing in some new
19 obstacle that was not part of the charge, but I think we
20 would be remiss in our responsibility if we didn't stop to
21 consider this. It is not just a person with a cold sore and
22 how he or she is going to feel in two and a half days; there
23 is really a different biologic context and a potential for
24 harm, even if that potential is small, which it may very
25 well be. It is a struggle, I think, for all of us.

1 DR. BRASS: In the interest of time, because I
2 want to get us done by 5 at the latest, there are three
3 other questions that were posed under the hypothetical, the
4 "yes" vote--one, "Please provide advice on the design,
5 conduct and monitoring of the post-marketing viral
6 resistance surveillance program." Two, "Please provide
7 advice on whether any additional Phase 4 studies are
8 needed." Three, "Please provide advice on any additional
9 labeling issues, including your recommendations for how
10 immunocompromised patients should be described in the OTC
11 label warning."
12 And again in the context of having the opportunity
13 to provide the agency input on a more global--
14 DR. KATZ: What I was going to ask is, in the
15 interest of time and also given the way the vote went, if we
16 could just focus on the surveillance program, because that
17 is something that we can look at even if we decide not to
18 take the product over-the-counter as a prescription product,
19 that would be helpful as to what kind of surveillance
20 program we might want to do.
21 DR. BRASS: We most certainly can limit our
22 discussion of that.
23 DR. MURPHY: And Dr. Brass, just because we may
24 lose more individuals on the committees, I did want to
25 comment, since you did vote down lines of the different

1 committees, to make sure the OTC committee realizes that
2 resistance is an increasing issue for FDA, and we are
3 looking at ways to address this in our labels and bringing
4 it forward, both in our education not only of physicians but
5 even of patients. So I did want to make that known to the
6 committees.
7 Thank you.
8 DR. BRASS: Thank you.
9 Comments on the surveillance program--or anything
10 else?
11 DR. McKINLEY-GRANT: Actually, since we aren't
12 going to discuss the additional labeling, can I just make
13 one comment and recommendation?
14 In terms of patients who have widespread eczema,
15 burn patients, patients who receive laser therapy, chemical
16 peels, anything that leaves open wide areas of the skin,
17 when they get herpes labialis, they are much more subject to
18 getting generalized herpes, and I think there should be a
19 warning for these patients--I am sure their physicians do
20 that, but perhaps not with the eczema patients or the atopic
21 dermatitis. It is not that uncommon, and I think a lot of
22 these patients need oral medicine as opposed to a creme, and
23 I think they should be aware of that.
24 DR. BRASS: Dr. Olivo?
25 DR. OLIVO: I'd like to make one comment about

1 surveillance, and it gets back to the question I asked Dr.
2 Whitley. If a surveillance program is set up--and I have
3 mixed feelings about the issue of tying over-the-counter
4 approval to a surveillance program--a surveillance program
5 is inherently a valuable thing to do, and to place it as a
6 carrot for OTC is to me perhaps a dangerous precedent.
7 Irrespective of that, if we set up a surveillance
8 program, I think we need to put some thought into how the
9 data that is generated from that program is going to be
10 utilized--in other words, in advance, some thought put into
11 if we get this result, what will we do with that result--
12 because otherwise it is going to be a delay in terms of
13 correcting our course if we are going down the wrong path.
14 DR. BRASS: Dr. Sachs?
15 DR. SACHS: In looking at the surveillance thing,
16 if I can make an analogy, there are some studies ongoing,
17 for example, for pneumococcal vaccine, where they said if
18 they got so many cases, they would stop the study and look
19 at it because it would help determine whether things were
20 useful. It turned out they got the cases, and they ended up
21 all being in the placebo group. So likely as in this, I
22 think either a number or percent of resistant or cases could
23 be a time to stop and look at all the data.
24 Other information that would be nice to have would
25 be what happens in recurrent users; why do they not refill

1 the prescription or use it again--is it that there was less
2 recurrence, is it that it didn't work, whatever it might be-
3 -maybe they didn't like the taste.
4 DR. BRASS: Other comments about the surveillance
5 program?
6 [No response.]
7 DR. BRASS: Okay. Dr. Jolson?
8 DR. JOLSON: I'll just ask, actually, a question
9 for the committee about surveillance and about setting just
10 what you proposed, which would be a threshold, to say that
11 above this, this would be unacceptable. Is the technology
12 at a point where we can realistically do that? In other
13 words, do we have enough confidence in these actual rates
14 that we could, in the future, say above "x" percent, this is
15 a significant increase?
16 DR. BRASS: Do any of our antiviral panelists want
17 to speak to that?
18 [No response.]
19 DR. BRASS: No expertise forthcoming to help you
20 with that.
21 DR. JOLSON: It's the end of a long day.
22 DR. BRASS: Yes, Dr. Diaz?
23 DR. DIAZ: Just one last comment in terms of the
24 surveillance. I think that making resistant disease
25 reportable would be something that would be useful in

1 addition to having in place a surveillance program, but
2 having any isolate that is obtained that is resistant be
3 reportable and clinical data obtained about that individual
4 would also go hand-in-hand with a surveillance program.
5 DR. BRASS: If there are no other comments from
6 the panel and no other issues from the agency, I thank
7 everybody for their participation, sponsors, guests and
8 panelists, and for maintaining a constructive and
9 interesting discussion.
10 Thank you.
11 [Whereupon, at 4:46 p.m., the proceedings were
12 concluded]

CERTIFICATE

I, ANNIE HAYES the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Annie Hayes

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