

1 are places where patient access to care is not what
2 it is here, and not what I want for me. And, isn't
3 that what this is really all about, the cost of
4 access to quality care?

5 AANMA surveyed 1200 members and
6 non-members via email. While the results are not
7 scientific, we found overwhelming concerns, best
8 summed up by this statement: Insurance companies
9 are trying to find ways to save themselves money.
10 If these drugs are put out over-the-counter we, the
11 consumer, will have to pay full price and not just
12 a \$5 or \$10 deductible. What will be next?
13 Self-help allergy testing kits and allergy shots
14 you can give at home? Allergies are serious,
15 especially when asthma comes into play. Drug
16 interactions will become more prevalent. We are
17 not doctors. It will get too confusing.

18 Nearly 100 percent of respondents believe
19 that the move to OTC labeling of non-sedating
20 antihistamines is a bad idea. They say it is
21 purely financially motivated on the part of
22 insurers and has nothing to do with patient safety.
23 As one person wrote, I am starting to become
24 depressed over insurance issues.

25 Where are the studies supporting consumer

1 self-guided allergy diagnostic skills? Where is
2 the research to support self-treatment and
3 self-taught pharmaceutical dispensing and mixing?
4 And, where is the real evidence that real people
5 will benefit from OTC status of non-sedating
6 antihistamines? There is no evidence to support
7 patients can safely use OTC non-sedating
8 antihistamines without a physician interaction.
9 So, please, do not support OTC status for
10 non-sedating antihistamines until there is. Thank
11 you very much for this opportunity.

12 DR. BRASS: Thank you. Our next speaker
13 will be Mr. Richard Carson.

14 MR. CARSON: Hi, I am Richard Carson. I
15 am Director of Chapter Relations and Public Policy
16 at the Asthma and Allergy Foundation of America,
17 AAFA, located here, in Washington, D.C. I do not
18 have any conflicts of interest regarding the issue
19 before the FDA and, for the record, I would like to
20 read aloud AAFA's statement that was submitted in
21 writing to the FDA.

22 Thank you for the opportunity to deliver
23 AAFA's statement on behalf of patients to this
24 panel. This will be brief. Thirty-eight percent
25 of Americans suffer from allergic diseases that may

1 require antihistamine treatment. Allergic rhinitis
2 alone affects 20 percent of the U.S. population and
3 contributes to the severity of asthma, sinusitis
4 and otitis media. Additional, allergic rhinitis
5 results in 3.8 million lost school and work days
6 annually.

7 Because of the huge impact on so many
8 people, the Asthma and Allergy Foundation of
9 America, AAFA, strongly supports the FDA's work to
10 assure the safety and efficacy of products
11 available to the public. Our Board of Directors is
12 concerned how the pending decision may impact a
13 patient's overall health, reasonable physician
14 oversight of potentially life-threatening
15 allergies, the availability of treatment options,
16 shifting economic burdens, and how these many
17 factors may impact their quality of life. The AAFA
18 Board of Directors, after extensive deliberation,
19 supports a thorough and data-driven process to
20 determine the impact on patient health outcomes and
21 whether patients are best served by moving
22 non-sedating antihistamines to OTC designation.

23 The Asthma and Allergy Foundation of
24 America is an independent, not-for-profit
25 organization whose mission is to improve the

1 quality of life for the 50 million people in the
2 U.S. with asthma and allergies through education,
3 advocacy and research. AAFA, through our national
4 office, state and local chapter network and
5 educational support groups, continues to educate
6 the American public about the seriousness of asthma
7 and allergic diseases; about the signs and sums of
8 these diseases, and encourages the importance of
9 seeking appropriate medical care for their
10 management. Thank you.

11 DR. RODEN: Eric, can I ask whether this
12 Foundation receives any pharmaceutical money?

13 MR. CARSON: We do get some in the form of
14 non-restricted educational grants.

15 DR. RODEN: So, that is a conflict.

16 DR. BRASS: Thank you. I have been
17 notified that Dr. Walson kindly donates his five
18 minutes back to me and, therefore, we will move on
19 to Dr. Luce.

20 Health Consultants

21 DR. LUCE: Good afternoon. My name is
22 Bryan Luce. I have a Ph.D. in Health Economics
23 from UCLA School of Public Health. I am the
24 immediate past president of the International
25 Society of Pharmacoeconomics and Outcomes Research.

1 Germane to the issue at hand, I served on the panel
2 on cost effectiveness in health and medicine that
3 advised the U.S. Public Health Service on cost
4 effectiveness methodology.

5 I am also the Chief Executive Officer of
6 MEDTAP International. MEDTAP is a health and
7 economics outcomes research firm whose client base
8 consists of the pharmaceutical industry and managed
9 care and governments around the world. My company
10 and I personally routinely do research for and
11 consult with Pfizer, Aventis and Schering, and we
12 have consulted with them on this particular OTC
13 issue. I hold no stock in any of the parties of
14 interest here and my time and expenses are paid by
15 my company.

16 I most appreciate the opportunity to
17 participate in this important debate. Please note
18 that my statement does not address whether
19 second-generation antihistamines should be
20 converted to OTC status, nor does it address
21 directly whether this class is sufficiently safe to
22 do so. My statement does address the issue as to
23 whether it is likely that conversion to OTC status
24 will increase the availability to allergy
25 sufferers.

1 As I understand it, this is an important
2 safety argument of the petitioner and is based, in
3 part, on the analysis of Dr. Nichol's model which
4 you heard earlier today. Dr. Nichol graciously
5 provided MEDTAP the opportunity to review the
6 spreadsheet and assumptions behind his model. So,
7 to that extent it was peer reviewed.

8 In our review of that model that we shared
9 with both Dr. Nichol and submitted to the docket
10 for the committee's review, we found that the
11 general approach of the model was appropriate; that
12 other elements needed to be added for completeness,
13 for example, benefits associated with a physician
14 visit or the issue of reduced productivity or
15 decreased productivity associated with sedation;
16 and we noted a number of concerns with the
17 assumptions. These concerns are important.

18 In the model, for instance, Dr. Nichol's
19 model estimated that 12 percent of allergy
20 sufferers seek physician treatment. Our
21 understanding from the 1996 national health
22 interview survey, that figure, instead of 12
23 percent, is 24 percent. Furthermore, in the model
24 there was the assumption that of the 12 percent
25 that seek physician service for allergy treatment,

1 80 percent actually are provided a
2 second-generation product. According to the 1998
3 national inventory medical care survey, instead of
4 80 percent, that figure should be 50 percent.
5 There are a number of other issues as well.

6 The key assumption, however, that I think
7 is germane to the issue at hand with respect to
8 safety of the Nichol model which addresses the
9 safety issue, is increased demand and, thus, access
10 to non-sedating antihistamines at the expense of
11 first-generation products is that the base case of
12 his model is a 67 percent price increase following
13 the OTC switch. That seems a gross overestimate to
14 us. The estimate is based on the price drop when
15 H-2 antagonists simultaneously switched from Rx to
16 OTC status, but it also came off patent which is
17 probably the biggest issue there.

18 The assumption of such a large price
19 reduction seems a major overestimate since all of
20 the second-generation antihistamines, as you know,
21 will still hold patents if you made a decision
22 today. In fact, I do not think it reasonable to
23 suppose that a post-OTC price of second-generation
24 products will approach the present out-of-pocket
25 exposure of the insured population. That position

1 has been made clear a number of times this
2 afternoon.

3 This exposure is a relatively modest
4 co-payment of \$10 to \$20, probably at the lower end
5 of that scale, as a matter of fact. If this is
6 true, presently insured allergy sufferers will, in
7 fact, face significantly higher out-of-pocket costs
8 for second-generation products post-OTC status
9 change. This will likely depress demand for the
10 insured group, not increase it. This is important
11 in that more than 80 percent of the U.S. population
12 is insured, a significant portion of whom have drug
13 insurance.

14 Further, my assertion is consistent with
15 economic theory and is consistent with empirical
16 evidence, not the least of which is the well-known
17 Rand health insurance experiment. Based largely on
18 what we believe is a faulty huge price reduction in
19 the base case, the model estimates a three-fold
20 increase in the use of non-sedating antihistamines
21 and a related decrease in the use of
22 first-generation products. It is this assumed
23 effect which drives the result of lower accident
24 rates.

25 In sum, we conclude that if

1 second-generation antihistamines were shifted to
2 OTC status use of these products would likely
3 decrease for the majority of the population who is
4 presently insured; may increase to some extent for
5 the minority of the population who is presently
6 uninsured; will likely not result in an overall
7 increase in the use of second-generation
8 antihistamines, and may well result in overall
9 decrease in the use of second-generation
10 antihistamines. Therefore, we do not think that
11 the case can be made, based on the present
12 analysis, that an OTC switch of second-generation
13 antihistamines will actually improve safety by
14 lowering accident rates. Thank you very much for
15 your time.

16 DR. BRASS: Thank you. Our next presenter
17 will be Dr. Hay.

18 DR. HAY: Good afternoon. Thank you for
19 allowing me this opportunity. My name is Dr. Joel
20 Hay. I am an associate professor in the Department
21 of Pharmaceutical Economics and Policy at the
22 University of Southern California School of
23 Pharmacy. I have a joint appointment in the
24 Department of Economics at USC.

25 In terms of disclosures, I have never been

1 an investigator for any of the antihistamine
2 products. I have done consulting with all three of
3 the manufacturers. My presentation was covered in
4 part by Aventis Pharmaceuticals. I have consulted
5 in the past with WellPoint Health Networks, and
6 have served on their pharmaceutical economics
7 advisory board. My wife works at WellPoint Health
8 Networks. I am a WellPoint consumer. I have a
9 Blue Cross card of California. I am a current
10 enrollee in Blue Cross. Our academic department at
11 USC receives research contract grants and funding
12 from many major managed care organizations and drug
13 companies, including both Aventis and WellPoint.
14 So, I can say that there is a good chance at the
15 end of the day that I may be facing either divorce,
16 unemployment or loss of health insurance.

17 [Laughter]

18 The FDA hearing request letter states that
19 the FDA is not seeking advice on economic
20 considerations of a switch. Rather, the FDA is
21 seeking advice from the committee on whether these
22 agents could be used appropriately and safely by
23 consumers without the intervention of a learned
24 intermediary.

25 In my view, public health and safety

1 issues often cannot be easily severed from economic
2 considerations, and in considering a non-sedating
3 antihistamine switch to OTC status there are unique
4 economic and market circumstances for this class
5 that may exacerbate public safety issues.

6 As I will discuss, the existing body of
7 literature suggests that such a switch may lead to
8 greater health risks for many Americans. The
9 evidence implies that those at greatest increased
10 risk are the poor, the frail elderly, the
11 uneducated and those with co-morbidities,
12 particularly asthma and sinusitis. There are
13 references for my assertions which are available in
14 my written statement.

15 First, a unique aspect of this citizen
16 petition to force an OTC switch needs to be
17 underscored. The public generally expects drug
18 prices to fall when a product goes to OTC status.
19 In this case, as Dr. Luce has pointed out, the
20 drugs still maintain patent protection and there is
21 no reason to assume that, as has happened in other
22 OTC switches, you will see much of a price
23 reduction.

24 In a discussion with a corporate executive
25 from Schering Plough, and I think Claritin is the

1 first product to lose patent protection, the
2 earliest date for uncontested loss of patent is
3 probably the year 2004. So, we are still looking
4 at a substantial period of time of patent
5 protection for all of these products.

6 Dr. Seidman was reported to have estimated
7 that the second-generation antihistamine switch
8 will save WellPoint Health Networks 80 million
9 dollars annually, but after such a switch Dr.
10 Seidman would tell California Blue Cross
11 subscribers, such as myself suffering from allergic
12 rhinitis, that Blue Cross does not cover OTC
13 medications. We will have to pay the \$2.00 to
14 \$2.49 per day out of our own pockets should we need
15 these second-generation medications, rather than
16 our current \$15 co-pay.

17 For those of us who are well off, well
18 educated and well informed, this will not be a
19 significant reason to avoid these products.
20 However, for the low income and the less educated,
21 including those currently covered by Medicaid,
22 Medicare managed plans, the Veterans
23 Administration, Indian Health Service and many
24 other third-party payers, there will likely be a
25 substantial switching from current covered

1 prescriptions that are second-generation
2 antihistamines to non-covered OTC sedating
3 antihistamines. You can buy generic
4 diphenhydramine for about 7 cents a pill or even
5 less.

6 It is well established that prescription
7 drug consumption is highly sensitive to price and
8 insurance coverage. Based on a study of Medicare
9 recipients, Stuart and Grana report that low income
10 elderly without supplemental drug insurance
11 coverage are 40 percent less likely to use
12 prescription medications than higher income elderly
13 with supplemental drug coverage. By eliminating
14 drug benefit coverage, this switch will increase
15 price and reduce demand for the second-generation
16 antihistamines. This, in turn, will increase
17 demand for the cheaper, sedating OTC medications,
18 particularly among those with low income or high
19 out-of-pocket medical expenses.

20 Allergic rhinitis affects more than 39
21 million persons in the United States. The U.S.
22 age-adjusted injury rate is 49 per 100,000. If
23 even 10 percent of these patients switch to the
24 sedating antihistamines we could see hundreds of
25 additional fatalities, not to mention non-fatal

1 injuries and loss in productivity and property
2 damage.

3 Let me make a point about the Canadian
4 situation. It has been underscored by Dr. Nader
5 that in Canada it is not truly OTC. It is, in
6 fact, a pharmacist consultation in terms of how you
7 get to use one of these products in Canada. It was
8 also mentioned by Dr. Spiegel that, in fact, in the
9 Canadian situation the rate of use of the sedating
10 antihistamines has increased. I am doing a totally
11 unrelated study to this issue on rates of
12 availability and prices for the most popular drugs
13 in the United States and Canada, ten prescription
14 and five OTC medications. Last week I just
15 finished surveying at random 43 pharmacies in
16 Vancouver, British Columbia and only 12 of those
17 pharmacies actually carried Claritin. They had all
18 the other drugs on their list but only 12 of the 43
19 had Claritin. So, I think we have to take the
20 Canadian experience with a grain of salt with
21 respect to this issue.

22 The other issue which has also been
23 addressed is co-morbidities but I see that my time
24 is running out. Thank you.

25 DR. BRASS: Thank you. The next speaker

1 will be Mr. Steve Francesco.

2 MR. FRANCESCO: Thank you. First of all,
3 I want to thank the FDA for this initiative. It
4 took a little bit of courage to be willing to press
5 the citizen's petition button, and my intention
6 this afternoon is to present my point of view. It
7 is my nickel and I would like my five minutes so
8 you can hear my two cents.

9 [Slide]

10 We, as a consulting firm in South Orange,
11 New Jersey, publish a newsletter called SWITCH. We
12 have a bias towards self-medication, and we have
13 subscribers around the world, mostly from
14 pharmaceutical companies. In 1998, we last
15 published a study which looked at Canada, the U.K.
16 and the U.S., and we predicted that there would be
17 a dual status switch in the United States in the
18 next few years. It was a 300-page study. So, in
19 that sense we are conflicted because we have people
20 who subscribe to the newsletter, we have people who
21 bought the studies and, moreover, we consult to
22 them as well.

23 [Slide]

24 Having said that, please remember that I
25 have said that this is my nickel. We do sell our

1 products and services to the healthcare industry
2 but today we are not here representing anyone. We
3 are here at our own expense to present our point of
4 view as industry experts on the subject of switch.

5 [Slide]

6 First of all, I would like to make it
7 perfectly clear that in our point of view
8 non-sedating antihistamines are definitely
9 OTC-able. Frankly, the discussion today I think
10 has tried to weasel around the fact that in many,
11 many markets these products have been without
12 prescription for many, many years. Canada was
13 1998; the U.K. was 1992; Germany was 1993. So, in
14 many, many respects these products are very, very
15 safe.

16 [Slide]

17 The second point is that the indication is
18 certainly OTC-able as well. The indications for
19 allergy are universally switched, and often they
20 are switched as hay fever, acute or seasonal
21 allergy; acute or seasonal rhinitis. So, the
22 indication discussion, in my view, is really quite
23 irrelevant. The fact is allergy is OTC in all
24 markets, including conservative markets like Japan.

25 [Slide]

1 And, these drugs are not OTC because of a
2 different distribution system. It has become very,
3 very clear over the years that a concept called a
4 third class of drugs which was launched really in
5 the U.K. in the early '70s, has not worked. Today
6 the pharmacist does not check in the U.K. or in
7 Canada for adverse reactions. They are too busy
8 counting pills. The medicines are too expensive so
9 that if you travel anywhere you will see that the
10 third class of drugs de facto does not work. This
11 has been supported by the fourth bullet point.
12 Your own general accounting office has studied this
13 and found that they do not work and they rejected
14 them here, in the United States. We, ourselves,
15 have done a lot of work in Europe and, again, the
16 third class of drugs really makes no difference.

17 [Slide]

18 So, what is the real issue that we are
19 debating today? In my view we are dealing with
20 gridlock.

21 [Slide]

22 We are dealing with the conflicting
23 mandates of insurance companies to reduce costs,
24 and that is their job. We are dealing with
25 pharmaceutical companies who wish to maximize their

1 profits, and that is their job. And, we are
2 dealing with the FDA who is interested in
3 maximizing public health, and that is their job.

4 So, we have here three conflicting
5 mandates and I am happy that this meeting was
6 called because maybe we can get some constructive
7 dialogue going.

8 For the sake of discussion, we have talked
9 about how insurance companies can save money. So
10 that is pretty well established and I won't spend
11 any time on that. We know the FDA is interested in
12 public health. Let me just give you one point on
13 the pharma companies, and I am going to
14 specifically cite Schering Plough. It is our
15 estimate that Claritin right now contributes
16 somewhere around 56 cents per share -- 56 cents.
17 This is specifically Schering Plough. If there
18 were a forced switch, the contribution on earnings
19 per share would go from 56 cents to about 6 cents.
20 That is a huge hit in terms of earnings per share.
21 That, in turn, would be a huge hit to the price of
22 the stock. That, in turn, could result in a
23 takeover. So, if you run the syllogism through, a
24 switch has pretty serious impact and they have
25 every reason to defend their territory.

1 [Slide]

2 In my view today, the panel cannot force a
3 switch even though products and indications are
4 very appropriate, even though non-sedating switches
5 save money, and there is a very good study that was
6 accomplished two years ago up in Canada. It is
7 unfortunate also because broader non-sedating
8 antihistamine access does reduce suffering. There
9 is a large population that has no insurance. There
10 is a large population that has no time to go to the
11 doctor. And, if you are a taxi driver, these drugs
12 allow you to work if you have an allergy.

13 [Slide]

14 Unfortunately, I don't think you are going
15 to be able to reach a decision today because the
16 pharmaceutical companies, in their own right, have
17 things such as patent protection. They have
18 intellectual property laws which will protect their
19 sponsors. So, what is going to happen over the
20 next couple of years, should there be a decision
21 against their will, is that the only one that will
22 benefit will be lawyers. There will be litigation
23 all over the place.

24 So, in my view, and I am being very
25 presumptuous here and I apologize if this offends

1 anyone, unfortunately, your likely conclusion will
2 be that these drugs are probably safe and effective
3 enough to gain OTC status but we need more data,
4 and you may not get it.

5 [Slide]

6 So, what is the real issue we are debating
7 today? Let's look at some facts. Fact number one
8 is there is little incentive to get pharma to
9 switch drugs earlier to the OTC market because of
10 profitability. It is that simple. There is no
11 incentive to take these products to the OTC market.
12 It is a bad business decision and they have
13 obligations to their shareholders.

14 Secondly, Waxman-Hatch, which was an
15 interesting attempt years back to extend patent
16 protection in order to gain additional research
17 funds, in fact frustrates an interest in switching
18 earlier because you give up your patent protection
19 with Waxman-Hatch if you switch before patent
20 protection. So, if you are in year five and you
21 could switch, and you could go out to year eleven
22 and then get three more years, you are going to
23 take year eleven as opposed to year five. If
24 Waxman-Hatch obstructs you this way a serious
25 discussion could have been that maybe the OTC

1 market is an incremental market. As it is, there
2 is very little incentive with Waxman-Hatch.

3 [Slide]

4 So, what are we dealing with --

5 DR. BRASS: I need you to finish up,
6 please.

7 MR. FRANCESCO: Yes. We are dealing with
8 a major flaw in our healthcare system, the
9 inability to maximally and responsibly get safe
10 drugs to the public. There is a need to get a
11 self-medication enhancer, not a life cycle
12 extender.

13 [Slide]

14 We need to develop dual status as a
15 concept which encourages public health. Patients
16 can be reimbursed. Consumers can buy if they want.
17 Pharma can expand their markets and insurance and
18 managed care can control costs more flexibly.

19 [Slide]

20 So, my conclusion is that I consider
21 non-sedating fine to switch, but we need to push
22 the dual status concept, gain legislative
23 mechanisms to encourage dual status and ensure that
24 there is understanding from the constituencies and
25 avoid gridlock.

1 [Slide]

2 Then we should turn to the following
3 indications. Thank you.

4 DR. BRASS: Our next speaker is Dr.
5 Spilker.

6 **Trade Organizations**

7 DR. SPILKER: Good afternoon. I am Bert
8 Spilker, Senior Vice President for Scientific and
9 Regulatory Affairs of the Pharmaceutical Research
10 and Manufacturers of America, or PhRMA. Each of
11 the three companies whose products are being
12 discussed today are members of our association, but
13 I would also state that our association does use
14 CareFirst or Blue Cross/Blue Shield.

15 The petition under review today seeks
16 unprecedented action by FDA -- the switch of
17 particular drugs from prescription to
18 nonprescription status over the clear, unambiguous
19 objections of the NDA holders concerning potential
20 safety issues about the individual drugs and their
21 use. A departure from the well-established model
22 would raise serious scientific, public policy and
23 legal issues. The legal and public policy
24 questions presented by the Blue Cross petition are
25 equally critical to consider before a decision is

1 made. PhRMA will address these important matters
2 in separate written comments to the docket.

3 It is highly desirable to develop
4 additional clinical data on a drug's use after its
5 approval under actual OTC conditions. Even though
6 we heard from the FDA today that this is not
7 absolutely mandatory or necessary, we say it is
8 very desirable and important. For example, will
9 consumers properly comprehend product labeling and
10 not self-diagnose and self-medicate if they
11 experience symptoms that should trigger a physician
12 consultation?

13 Significant safety issues can arise under
14 OTC use that do not exist or are of considerably
15 less concern when a drug is used in accordance with
16 a physician's prescription and supervision. For
17 example, a drug may present possible drug
18 interactions that a physician could identify and
19 manage if more closely monitoring a patient. It is
20 wholly inappropriate to consider a switch on the
21 basis of conclusory assertions or on the basis of
22 anecdotal, non-peer reviewed meta-analyses, or
23 otherwise limited safety data.

24 Drug manufacturers themselves have the
25 most comprehensive and most detailed knowledge of

1 their drugs. These firms are in the best position
2 to decide whether to invest in the development of
3 additional information necessary to support a
4 switch, and at what rate over time this investment
5 should occur. A third party does not have the same
6 expertise or experience with the drug and is,
7 therefore, not able to assess whether a switch is
8 premature and would expose the public to health
9 risks.

10 For these reasons, evaluation of a switch
11 without the sponsor's full cooperation and
12 involvement is highly problematic. It could lead
13 to exposing patients to drug risks before they are
14 adequately assessed. For example, the Seldane
15 experience is relevant and a cautionary tale for
16 all of us.

17 Forcing a manufacturer to sell a drug
18 over-the-counter risks disrupting the drug
19 development process. That statement is so
20 important I am going to repeat it for your benefit
21 -- forcing a manufacturer to sell a drug
22 over-the-counter against their clear wishes risks
23 disrupting the drug development process. This
24 decision would be a major and unprecedented change
25 from U.S. drug development practices today.

1 Sponsors carefully establish research plans and
2 development strategies for a product's full life
3 cycle, and these plans would be disrupted in a
4 serious way by unanticipated switches mandated by
5 FDA or via requests from a third party.
6 Introducing uncertainty into the drug development
7 process about possible OTC switches would
8 significantly complicate the already different
9 considerations that underlie a company's decision
10 to proceed with drug development, and could chill
11 many areas of research and development.

12 Further, we do not believe the U.S.
13 government has the ethical right to interfere in
14 these decisions. Whether the government has the
15 legal right will be left to discuss at a later
16 time.

17 The issue of Canadian OTC regulations has
18 been raised today, but there are significant
19 differences between our two countries. For
20 example, one can buy drugs with an eighth grain
21 codeine in Canada as an OTC but not here, in the
22 state that we are presently situated in.

23 This petition cannot be viewed in
24 isolation. Granting switches proposed over the
25 sponsor's clear objections would be a major change,

1 and if the FDA agrees to these switches this will
2 be the tip of the iceberg. What classes of drugs
3 will be next? What classes of drugs will be
4 exempt? Once the bell has been sounded inviting
5 third parties to prompt such switches, it will be
6 impossible to un-ring and who is to say which
7 groups can request such changes and who cannot? It
8 is likely that many products will be proposed for
9 such changes of status on a very frequent basis by
10 those people and groups who have a strong self
11 interest in this change. Thank you for your time
12 and attention.

13 DR. BRASS: Thank you very much. It is my
14 understanding that Dr. Maves has also yielded his
15 time back to the committee. At this point, I would
16 like to continue the question sessions that were
17 initiated this morning. We had presentations by
18 both petitioner, manufacturer and the FDA and I
19 would ask that questions be directed specifically
20 to one of those parties or, if it is a general
21 question, simply posed to whoever might want to
22 answer it. So, we are now open for questions.
23 Yes, Dr. Lam?

24 **Committee Discussion**

25 DR. LAM: This is a question for the

1 manufacturer. Given the FDA report, I am
2 interested in terms of what would be your
3 perspective as to how much safety data is
4 necessary, over what time frame in terms of
5 supporting a switch regardless of who initiates the
6 switching process.

7 DR. SPIEGEL: Can I have the last part of
8 your question again?

9 DR. LAM: Given the report by the FDA, I
10 am interested to learn about your perspective as to
11 how much safety data is necessary, over what time
12 frame, in order to support the switching process,
13 regardless of whether the switching process is
14 initiated by an insurance company or by the
15 manufacturer.

16 DR. SPIEGEL: Well, we actually believe
17 that what the FDA has presented is very consistent
18 with our own perspective on our drug. They have
19 shown this morning that under the conditions of
20 prescription use under a physician Claritin is a
21 very safe product, and we agree with that. I think
22 the burden of proof is on whoever the petitioner is
23 or on the FDA. We believe we have a very safe
24 product under the use of a prescription product and
25 under a physician.

1 I also think it is somewhat ironic that
2 the FDA is saying we don't have to take into
3 account current science, that you can be asked to
4 go back to a monograph that was approved more than
5 15 years ago, and ignore the fact allergies have
6 changed and the understanding of allergies has
7 changed since then.

8 DR. BRASS: Dr. Wood?

9 DR. WOOD: I have two questions and I
10 would like to ask them separately. The first one
11 is actually a procedural one addressed to the FDA.
12 It seems to me that what we have had today is a
13 sort of unseemly parade of people presenting to us
14 to protect their own financial interests, and sort
15 of none of us come here with clean hands, including
16 all of us because I don't want to pay for my drugs
17 either.

18 But, as I understand it, and this is the
19 question, we are not here to consider the real
20 financial interests that apply in this setting and
21 the real financial pain that people may suffer but,
22 rather, we are here to consider whether these drugs
23 should be switched to over-the-counter based on
24 issues of safety, and based on issues of ability to
25 self-diagnose, and based on issues of relative

1 merit versus other therapies. Is it the case,
2 therefore, that the only issues that you want
3 advice from this committee on is whether the drugs
4 are appropriate in terms of safety, appropriate in
5 terms of ability of patients to diagnose their
6 condition, and that is it?

7 DR. MEYER: Yes.

8 DR. WOOD: Okay. So, whatever other
9 issues are on the table that we have heard a lot
10 about we should pass over and ignore. Is that
11 right?

12 DR. MEYER: They are not issues that we
13 are seeking advice on.

14 DR. WOOD: The second is a more pointed
15 question. One of the issues that has been raised
16 relates to the apparent relative lack of experience
17 with fexofenadine, but it seems to me that there
18 is, in fact, a huge experience with the molecule
19 fexofenadine given that it is the active metabolite
20 produced by terfenadine. We heard there is 24
21 million patient years of experience with
22 terfenadine. It was withdrawn from the market
23 because of a single problem, its cardiac effects
24 which seemed to be unique to that molecule in
25 contrast to fexofenadine. So, wouldn't you think

1 that there is probably more experience with
2 fexofenadine than almost any molecule that has been
3 considered for an over-the-counter switch?

4 DR. MEYER: I am not sure I would
5 necessarily say more experience but I think your
6 other points are very articulated. I tried to make
7 that kind of observation during my talk but perhaps
8 it was not as articulate a case as you just made.

9 DR. BRASS: Dr. Neill?

10 DR. NEILL: I am interested in
11 manufacturers' response to the question about what
12 specific safety issues you have that you feel make
13 your products inappropriate for OTC marketing, and
14 if you have specific safety concerns how would you
15 design studies to address those concerns in the
16 event that any of you in the future might bring
17 these to OTC? What type of study? How many
18 people? How long?

19 DR. SPIEGEL: Thank you for the
20 opportunity to elaborate on some of the points I
21 made briefly in the presentation this morning. The
22 point we were trying to make is that there is a
23 body of evidence that speaks to the pharmacologic
24 safety of the molecule. As you have heard from
25 many speakers, including representatives of the

1 professional allergy and otolaryngology
2 associations, there is a very significant issue
3 that has been raised and that people are concerned
4 about, which is the potential for misuse,
5 misdiagnosis, and for patients not to take it
6 properly and get into trouble --

7 DR. NEILL: I am going to interrupt
8 briefly --

9 DR. SPIEGEL: Sure.

10 DR. NEILL: -- because the FDA has
11 instructed me that I should not consider whether or
12 not allergic rhinitis is a self-diagnosable
13 condition, given that as an OTC condition it is
14 OTC. So, aside from that concern, do you have
15 specific concerns about your products that raise
16 specific safety issues related to their use in the
17 OTC setting absent the ability of a person to
18 self-diagnose?

19 DR. SPIEGEL: I think the committee in its
20 deliberations today is going to have to ask itself
21 with no data provided on OTC use for you to see
22 what is the incidence of mis-dosing, which is a
23 safety issue, and getting into trouble because of
24 delays in seeking medical care for complications of
25 the allergic rhinitis -- you have no information to

1 know how often that happens. Does it happen in 2
2 percent, 10 percent or 20 percent of patients? We
3 consider that a safety issue.

4 DR. NEILL: I am asking you because your
5 representative from PhRMA just told me that the
6 manufacturers have the largest body of data related
7 to the safety of these components. I understand
8 that because you have not made the request for OTC
9 that there haven't been label comprehension or
10 actual use studies and, yet, it has been suggested
11 that those are neither required in all instances
12 nor, even if you were to request OTC status would
13 it be demanded that you have them. I am also a
14 veteran of enough of these meetings to understand
15 that when industry has requested these switches
16 there have often been many entreaties on the part
17 of the manufacturers for us to consider those
18 studies nearly dispensable.

19 DR. SPIEGEL: Well, it is my understand
20 that this committee has in recent years seen a new
21 level of rigor and scientific quality that is
22 expected of a sponsor when they bring forward a
23 petition from the sponsor that includes actual use
24 studies. There has been in recent years a new
25 evolution of scientific expectations of what you

1 can test in an OTC-like setting that establishes
2 usage patterns that give you an idea of what might
3 be most likely to happen.

4 As far as your first question, I don't
5 want to sound like a broken record but I think we
6 believe our large experience has been obtained
7 around the world, mostly under prescription use,
8 and I would like to just again put that into
9 perspective. Claritin has been approved in over
10 100 countries around the world. In 90 of them it
11 has prescription status, and in very few is it
12 anything close to a U.S. OTC system.

13 DR. BRASS: Dr. Joad?

14 DR. JOAD: If both companies could
15 completely finish answering Dr. Lam's question, the
16 question is how much post-marketing information
17 would you feel would be adequate to have it go OTC?

18 DR. NADER: Thank you for the opportunity
19 to address this very important question. Before
20 answering it directly, Mr. Chairman, I would like
21 to introduce three of our scientists who are here
22 with us to answer very specific technical
23 questions. We have Dr. Geising, who was one of the
24 grandfathers or godfathers of the developing
25 fexofenadine. He is currently the head of global

1 pharmacokinetics and pharmacology with our
2 organization. We have Dr. Paul Legerin, who is the
3 head of global pharmacoepidemiology and
4 pharmaco-vigilance, and Dr. George Georges, who is
5 in charge of our Allegra medical research program.

6 To more specifically answer your question,
7 the answer is I don't know. I will qualify my
8 answer by putting the fexofenadine experience into
9 perspective. Fexofenadine has been on the market
10 only for five years, and at the specific request,
11 and working with the FDA, it was developed as a
12 novel product. Now, let's put fexofenadine into
13 perspective, and I would like maybe to have slide
14 nine, with your permission.

15 [Slide]

16 This slide simply shows the examples of
17 serious regulatory actions over five years after
18 launch. We have a list of products where the FDA
19 had to take very serious actions over five years
20 after launch.

21 [Slide]

22 If I take, for example, the next slide,
23 which is slide ten, it simply says or shows the
24 difference of the length between the year of launch
25 and the year when the drug was approved as OTC.

1 Granted, these are different classes of drug but no
2 one on the list there is just five years with 4.7
3 million years exposure.

4 So, we need to continue monitoring our
5 post-marketing experience, and this is my answer to
6 your question, and look at signals; work with the
7 FDA; work with our global pharmaco-vigilance team;
8 and carefully look at any signal or any safety
9 events that would be of any concern.

10 DR. BRASS: Dr. Kelly?

11 DR. KELLY: Thank you. I am going to try
12 to focus my question on safety. I would like to
13 thank the agency for providing I think an excellent
14 and succinct evaluation of the post-marketing
15 safety. But I agree with some of the professional
16 organizations in that safety of therapy also
17 involves use and misuse of various therapies, and
18 inadequate use.

19 The question came up a lot about potential
20 for non-adherence, increased use or excessive use
21 of drugs when not prescribed by the physician.
22 And, my notice of that was that it was all opinion,
23 and that there was very little data to support
24 either side. I would like anybody from the
25 professional organizations, either Dr. Lanier or

1 even Dr. Rachelefsky over there, to tell us whether
2 there is any data involved in looking at adherence,
3 compliance, and misuse of these drugs in a
4 nonprescription realm versus a prescription only
5 realm.

6 DR. LANIER: Dr. Kelly, I will give you
7 the best that we can in that when you are talking
8 about medications of this nature for chronic
9 disease, you generally talk about, from a
10 compliance standpoint, less medication rather than
11 more. It is not often that people would use
12 excessive amounts of antihistamines. In this
13 particular case, the problem is that people stop
14 and start a medication which probably should be
15 used on a regular basis. Some of the compounds
16 require several days before they get a steady
17 state, which is a little bit of a concern if you
18 don't do it as a physician suggests, and we know
19 that people on OTC basis stop and start very
20 regularly. So, the compliance data is poor as it
21 is with any disease, and it primarily exists as
22 under-use as opposed to an overuse.

23 DR. KELLY: To be more direct, is there
24 any evidence that because you are getting it by
25 prescription that is any different?

1 DR. LANIER: No data to my knowledge. My
2 instinct would be that when a physician tells you
3 an instruction and tells you to take a pill every
4 day that you are probably somewhat more likely to
5 take it than the other way. I only say somewhat
6 more likely because we know that compliance is
7 terrible what the directions are.

8 DR. RACHELEFSKY: I am Gary Rachelefsky.
9 I am here on behalf of Schering Corporation and I
10 have been a consultant for all three companies. I
11 am on the speakers program and have done clinical
12 trials of all three. I am past president of the
13 American Academy of Allergy, Asthma and Immunology.
14 I am co-chair of the allergic task force that
15 developed the allergy report, and I can go on and
16 on with my qualifications.

17 DR. KELLY: That is all right, answer the
18 questionz!

19 DR. RACHELEFSKY: Well, I don't like the
20 word compliance. I will answer it better by using
21 the word adherence because that is the real key to
22 the message here. When the patient and the doctor
23 partner with a care plan, then the adherence, the
24 taking of the medicine and the following through
25 with the treatment plan is much more significant.

1 I have developed data on that. There is lots of
2 literature on that. And, I think the issue here
3 and what I think you are alluding to is when there
4 is a partnership between the patient and the
5 healthcare provider, say someone who has allergic
6 rhinitis and sinusitis, then you get a much better
7 outcome. When you have a patient with allergic
8 rhinitis and asthma and there is no recognition and
9 no contact and discussion between the parent, the
10 family and the patient the outcome has got to be
11 worse. It has to be. You know, the answer I think
12 is intuitive. Does that address your question?
13 There are no specific studies to answer your
14 question, but I take care of 4000 active patients
15 and I have been doing this for 27 years, and I know
16 from my own personal experience, though it is
17 anecdotal, that when a physician is taken out of
18 the realm of care the patient suffers.

19 DR. BRASS: I just want to make a comment
20 about Dr. Kelly's question to help explain why we
21 are not going to discuss those issues in great
22 depth, and that is because we have not been privy
23 to the data one way or another. In contrast,
24 previous panels and the FDA have reviewed in detail
25 the data that support or don't support whether

1 allergic rhinitis and allergic related conditions
2 are, in fact, self-diagnosable and treatable. We
3 may disagree with those past judgments and there
4 may, in fact, be new data. The problem is we
5 haven't seen it and have no basis for re-addressing
6 an issue that has been evaluated on a scientific
7 basis extensively in the past. Dr. D'Agostino?

8 DR. D'AGOSTINO: I wanted to pursue a bit
9 in terms of what it is that we are talking about in
10 terms of the OTC switch. The label that is being
11 suggested as a possibility looks like the first
12 generation, yet, the presentations that were made
13 by the sponsor -- and I would like the sponsor to
14 address it -- emphasized the chronic use aspect and
15 the complex patient, and so forth. So, are you
16 worried that if you put it on an OTC basis there
17 will be a lot of off-label use being carried into
18 the OTC market? Or, is it really not off-label use
19 that is actually going on but, somehow or other,
20 the vocabulary is not clear enough that there is a
21 chronic versus a short-term type of activity going
22 on, short-term with the first generation and maybe
23 long-term for the second generation?

24 DR. SPIEGEL: My first answer is similar
25 to my colleague -- I don't know. We don't have

1 data; you don't have data. You asked a question
2 earlier this morning about how real is this
3 characterization that there are chronic and there
4 are acute uses of the antihistamines. Again, it is
5 not scientific but we do know that the average
6 Claritin user gets a prescription that lasts for
7 two and a half months. So, we believe that those
8 patients are taking it chronically every day. We
9 know that for the over-the-counter products the
10 most common presentation is a 24-pack of capsules
11 that can be used every 4-6 hours. So, that would
12 be for more short-term use.

13 Beyond that, I think in the last 10, 15
14 years the appreciation of the co-morbidities that
15 we talked about and that others have talked about
16 have come about since the monograph was initiated
17 15 years ago and since it was finalized more than
18 15 years ago. There is a new understanding that
19 allergies are not trivial; that they are very
20 commonly associated as part of a complex condition.

21 DR. D'AGOSTINO: So, the objective of an
22 actual use study for first-generation antihistamine
23 would be quite different than an actual use study
24 for the second generation given the two and a half
25 month use versus a two day use.

1 DR. SPIEGEL: I think an actual use study
2 could be developed that would characterize the
3 actual use pattern of the second generation. We
4 haven't thought about what it would look like
5 compared to the first.

6 DR. BRASS: Dr. Roden?

7 DR. RODEN: I have a couple of questions
8 and I just want to preface them by saying that I
9 have been on panels for about five or six years and
10 I have never, to use the PG-13 word, seen a higher
11 titer of disingenuousness around the table than
12 this. I won't go on and use the R-rated word but
13 you can all figure out what that is. It starts
14 with a B.

15 My comment is sort of directed at the FDA
16 and I don't think requires a response, and that is
17 it seems to me that there is a reductio ad absurdum
18 at work here, and that is if a sponsor were to
19 develop a compound that was safe and effective for
20 a highly important unmet medical need and could
21 show that it was totally safe, then you are in the
22 awkward position of being subjecting yourself to
23 moving a drug such as that to over-the-counter use
24 earlier than a drug that is widely recognized as
25 not so safe, thereby penalizing sponsors for

1 developing better drugs. That doesn't require a
2 response but it is something to think about as you
3 deliberate in your decision-making after we make
4 our vote.

5 I do have two specific questions for the
6 pharmaceutical sponsors. The first is to Dr.
7 Nader. You have told us several times now that it
8 is very important that we continue to accumulate
9 more data on effects of fexofenadine and its
10 safety. I agree with Dr. Wood that there is a
11 very, very large body of safety data on
12 fexofenadine but I am very interested in hearing
13 from you specifically what kinds of studies you
14 have ongoing now to develop more safety data, in
15 particular with respect to intensive
16 pharmaco-vigilance beyond looking at what people
17 report to the FDA or other data bases in this
18 country or in a Third World country like Canada or
19 the United Kingdom.

20 [Laughter]

21 I am Canadian so I should take offense at
22 the Third World part.

23 DR. NADER: I am Canadian as well so I
24 won't take it personally.

25 [Laughter]

1 DR. RODEN: Vous parlez francais?

2 DR. NADER: Tout a fait.

3 [Slide]

4 It is very different in such a short time
5 really to go over all our programs, but I will give
6 you just a sample -- that may not be the
7 appropriate word here but just a view of our
8 programs.

9 [Slide]

10 This slide summarizes our work on
11 pediatrics.

12 [Slide]

13 We have a number of development programs
14 ongoing in Japan. Fexofenadine was approved in
15 Japan very, very recently. We are continuing to
16 characterize the drug in the Japanese population.

17 [Slide]

18 This is a program that we have in new
19 formulations, three different programs. But also
20 to answer your question, we have a number of trials
21 going on related to safety and effectiveness, the
22 traditional Phase IV post-marketing trials that are
23 not on this slide. We have literally hundreds --

24 DR. RODEN: Could you expand on the
25 traditional Phase IV post-marketing trials and how

1 that is going to generate new safety data that you
2 seem to think is required before anybody can go
3 forward with this application?

4 DR. NADER: The traditional Phase IV
5 safety data that we are working on include at least
6 three different categories. Number one, we are
7 looking at a subpopulation or specific population
8 to see how the drug interacts in those specific
9 populations. The second group of trials includes
10 large post-marketing effectiveness trials where
11 this drug is used in a wide variety of different
12 populations as part of the clinical practice. The
13 third is a comparative trial to the current doses
14 and current formulations and current competitors.
15 In every one of these trials we are collecting
16 adverse events through the case report form and
17 reporting to the FDA.

18 DR. RODEN: That answers my question. In
19 my view, that is not expanded pharmaco-vigilance.
20 That is just Phase IV post-marketing studies that
21 seem pretty ordinary to me.

22 I have a question for Dr. Spiegel. Dr.
23 Spiegel, you alluded several times to the fact that
24 the allergy landscape has changed completely, and
25 that is why it isn't appropriate for us to even go

1 forward with this consideration. Can you expand on
2 that a little bit, particularly with respect to the
3 studies that form the basis of the current approval
4 of Claritin. Were they conducted in the new
5 allergy environment or in the old allergy
6 environment? If they were conducted in the old
7 allergy environment, are you suggesting that
8 approval should be withdrawn and studies redone in
9 the new allergy environment?

10 DR. SPIEGEL: The basis of our original
11 application was primarily based on studies in SAR
12 using criteria that already existed and using
13 endpoints for relatively short studies. We have
14 also conducted studies in perennial allergic
15 rhinitis that have gone as long as six months to
16 establish safety and efficacy in longer-term dosing
17 as part of our formal clinical trials.

18 We have also initiated, as I believe
19 Aventis has, studies to look more specifically at
20 the effects of treating allergy in patients with
21 asthma, but that has not resulted in a claim yet
22 for labeling.

23 DR. BRASS: Dr. Sachs?

24 DR. SACHS: My question is actually
25 directed to either the FDA or to manufacturing

1 concerning safety. Two points or two questions.
2 Poison control data, has that been reviewed for
3 either?

4 DR. MEYER: We have not done that as a
5 part of our review. That is, unfortunately,
6 expensive proprietary data.

7 DR. SACHS: Because actually that seems
8 like a very practical way to assess safety
9 independently of the regulatory boards, I guess.

10 DR. MEYER: I would say that undoubtedly
11 if one were going to do a real comprehensive look,
12 you would probably take advantage of all the data,
13 including such data. Those data though do not
14 routinely add a lot because of the sort of
15 anecdotal nature of the way that they are tracked.
16 That is not disparaging of the people who do a very
17 good job at poison control, but the data collection
18 for that has a very different intent from rigorous
19 safety evaluations of drugs.

20 DR. SACHS: On the other hand, as someone
21 has said on this committee for a couple of years,
22 that is usually data that is quite helpful in the
23 overall safety scheme.

24 It does look like there are some signals
25 though for problems with these medicines, although

1 I do use them for the kids that I see as a
2 pediatrician with lots of counseling --
3 specifically seizures and cardiac effects. The one
4 question I have is there was some allusion -- and
5 this is just for my perspective -- that there was a
6 signal from Seldane when it was early approved,
7 that there might be a problem. And, since we are
8 seeing some signals, I am just curious about the
9 relative strength of the signal we are getting from
10 these medicines as opposed to Seldane.

11 DR. MEYER: Right. I would like to stress
12 that one of the actions taken with Seldane was with
13 an advisory committee, within five years of its
14 marketing, to actually talk about the safety signal
15 and to address it in terms of safety, labeling and
16 so on. The signals we saw here, again, are not of
17 a nature that would lead us to reconsider whether
18 these drugs should be available at all, nor
19 substantive changes in the labeling beyond what is
20 already in the labeling. So, we are really talking
21 about whether these signals really have any meaning
22 to the discussion about the OTC availability or
23 potential OTC availability of these drugs.

24 Again, I think I would like to stress that
25 these are not signals that worry us otherwise. If

1 you had a very significant cardiac effect, a la
2 what was seen with terfenadine, we would be talking
3 about an approvability issue altogether, not just
4 whether the drug should be OTC versus Rx.

5 DR. LEGERIN: Paul Legerin,
6 pharmaco-vigilance from Aventis. I just wanted to
7 take the opportunity to make a clarification with
8 the Seldane story. The drug was actually initially
9 marketed in Europe in 1981 and there was
10 substantial market exposure prior to the 1990 FDA
11 advisory committee looking at the initial signal.
12 In fact, out of the 24 million patient years of
13 exposure, the bulk of that, about 18 million
14 patient years of exposure, had occurred prior to
15 the identification of the signal, which gets to our
16 point basically that some of these signals are not
17 easily identified and take some time, as well as a
18 significant volume of patient exposure on the
19 market to be able to identify such critical
20 signals.

21 DR. JENKINS: I think we have to follow
22 that up. The cardinal safety problem st
23 terfenadine was a very specific cardiac arrhythmia
24 Torsade de pointes. When you look at terfenadine,
25 all the pieces fit the puzzle, the in vitro studies

1 with the ion channels; the myocyte studies in vitro
2 fit; the animal studies fit once we went back and
3 looked at that data; the clinical data fit. If you
4 give a patient a dose of terfenadine that is only a
5 few times higher than the recommend dose at the
6 time you saw a QT prolongation even in normal
7 patients. So, the whole package fit together that
8 would had a problem with cardiac repolarization
9 with terfenadine. All three of these drugs have
10 been carefully evaluated for those effects on
11 cardiac repolarization and the findings are absent.
12 So, you have to put it all together in a package.
13 It is not just the terfenadine experience. We
14 learned from the terfenadine experience. We
15 applied that information to the subsequent three
16 drugs and, in fact, that is why we have
17 fexofenadine because we learned that fexofenadine
18 was not the bad actor in the terfenadine
19 experience, and that is why the studies that were
20 done with fexofenadine turned out to be negative.
21 It is not apparently involved in cardiac
22 repolarization abnormalities. So, it is a
23 different package than what you are talking about
24 with terfenadine.

25 DR. SACHS: My point was actually

1 necessarily to compare Seldane. The point really
2 was we are always asked about safety and efficacy
3 and, you know, show that there is really clear
4 benefit on both points to switch something to OTC
5 and the criteria have always seemed to be slightly
6 more rigorous than getting approval for use in the
7 prescription field. I think my perspective also
8 comes from the experience with the rotashield virus
9 vaccine. Again, there was a signal in the original
10 data to show there was a complication that was not
11 really realized until it was used more widely.
12 Granted, it was recognized very quickly, and I
13 think that is a plus for the way we look at
14 medicines and drugs in this country and follow
15 them, and my concern is I do not feel, at least so
16 far, that I am getting a lot of the safety data
17 that I am used to seeing for going OTC.

18 DR. BRASS: Miss Conner?

19 MS. CONNER: A question for Dr. Meyer
20 probably or maybe Dr. Jenkins. Since the majority
21 of applications for OTC switch are generated by the
22 pharmaceutical companies or manufacturers, can you
23 give me, for my own edification, any indication of
24 what percentage of those applications occur before
25 the drug is due to go off patent?

1 DR. JENKINS: I don't have data I can
2 point to. Clearly, a lot of those applications are
3 submitted near the end of the patent life or the
4 exclusivity life of the product. You may want to
5 let the pharmaceutical industry provide their
6 explanation for why that happens. Maybe they
7 believe that it takes that long to get the safety
8 data that they think they need. Whether it is a
9 financial consideration, I can't answer, but you
10 are right in observing that many occur near the end
11 of patent life.

12 MS. CONNER: Thank you.

13 DR. GANLEY: I will just add to that. One
14 of the things that has been brought up today is
15 this need for an actual use study, and in our
16 regulations if a study is required in an NDA
17 supplement, in this case switching from
18 prescription to OTC, if there is a new essential
19 study performed it may make them eligible for
20 additional exclusivity. So, as they get close to
21 the end of their patent life and generics will
22 become available, if they can do a study to take it
23 OTC they could extend that by three years.

24 DR. BRASS: Dr. Fink?

25 DR. FINK: Well, Dr. Kelly asked my

1 primary question so I will try a secondary question
2 and I think I will address it to Dr. Spiegel. It
3 is a two-part question. What is the amount of
4 money that is currently spent on drug to consumer
5 advertising versus physician education about
6 Claritin?

7 DR. BRASS: You don't have to answer that
8 if you don't want to. Again, the financial
9 considerations are not the basis, or their
10 behaviors, or anything else. Again, if the sponsor
11 would like to make a contribution -- but I really
12 think that is tangential to the focus.

13 DR. FINK: Well, let me explain the second
14 part of the question, it would appear that the
15 pharmaceutical manufacturers feel that these drugs
16 are safe enough to probably be spending more money
17 on direct to consumer advertising about the drugs
18 than physician education. And, if they had major
19 safety concerns, one would think it would be
20 appropriate for them to be spending more money on
21 physician education rather than direct to consumer
22 advertising.

23 DR. SPIEGEL: Well, I will give a one-part
24 answer. I really don't know the actual numbers. I
25 think we have been consistent in saying in every

1 advertisement that we have used, which are reviewed
2 by the FDA as well, we end by saying talk to your
3 doctor; see your doctor. And, we think that is a
4 consistent message to educate people about
5 allergies and tell them to talk to their physician.
6 That is consistent with everything we have said
7 today.

8 DR. BRASS: Dr. Blewitt?

9 DR. BLEWITT: It is a question for Dr.
10 Meyer and it follows through somewhat with Ralph's
11 line of thinking. In your comment that you have
12 determined that neither an in-home use study or a
13 label comprehension study is necessary for the
14 switch proposed, and I have long been an advocate
15 of switch and I have watched this evolution over
16 the past decade the FDA requests, if not
17 requirements for label comprehension studies, for
18 actual use studies and I can't understand why the
19 agency wouldn't want to develop the kind of
20 information that can be obtained from studies of
21 that sort here. I mean, what is to be lost? I
22 think there is more to be lost than to be gained.

23 For instance, you have mentioned FDA's own
24 limitations of the data. You have the
25 antihistamine working group that has mentioned that

1 the need to demonstrate -- my words -- the
2 consumer's ability to understand and use these
3 products in an OTC setting, and that hasn't been
4 demonstrated at this point, and I don't understand
5 why you wouldn't want to do that.

6 DR. MEYER: First of all, I do want to
7 stress that I chose the word "necessary" advisedly.
8 I think that what we are talking about here is not
9 the switch of a new indication or a new class of
10 medications. What we are talking about is a
11 members of a class that are already available
12 over-the-counter. If there were unique
13 characteristics of these drugs either in their use,
14 particularly as they relate to safety, or other
15 characteristics of these drugs, then I think it
16 would be necessary to do an actual use study. But
17 if we already have over-the-counter antihistamines,
18 if we already accept under the monograph process
19 and under NDA switch proposals that have been
20 brought in by manufacturers in the past for what
21 correctly could be called second-generation
22 antihistamines, such as Tavist, I guess our
23 viewpoint is that you don't strictly need an actual
24 use study. We think that it has already been
25 established that consumers can reasonably diagnose

1 themselves as having allergic rhinitis and
2 reasonably use antihistamines in that setting. We
3 are never opposed to getting more data, however.

4 DR. JENKINS: Let me follow-up on that
5 answer also, please. We had a switch candidate
6 that came before these two committees several years
7 ago for chromolyn sodium. In that case the FDA did
8 require an actual study for that product, not
9 because it was an allergic rhinitis indication but
10 because it was a different type of product to take
11 over-the-counter for an allergic rhinitis
12 indication. It was a product that for efficacy
13 required chronic and continuous use. That product
14 also had a prevention claim which was unique for
15 the over-the-counter marketplace. So, we did ask
16 and required an actual use study for chromolyn
17 sodium when the manufacturer came and requested
18 that over-the-counter switch. That was not based
19 on the fact that they were asking for allergic
20 rhinitis. That was based on the fact that it was a
21 new class of molecule, a new type of use, and we
22 did learn from that. I would echo Dr. Meyer,
23 antihistamines and the diagnosis of allergic
24 rhinitis and use of antihistamines over-the-counter
25 is not new. That is why we don't feel a study is

1 necessary.

2 DR. BLEWITT: Yes, and I would simply
3 suggest that there actually is a difference. In my
4 own mind, I see this almost as a new indication and
5 that is conditions of use because what we are
6 seeing now is conditions of use in a prescription
7 environment and we don't know the conditions of use
8 in an OTC environment. Until you develop that kind
9 of information I don't know how you can be
10 comfortable with simply switching it
11 over-the-counter.

12 DR. JENKINS: Can I ask what the basis
13 would be of your assumption that it would be
14 different than the currently marketed
15 over-the-counter antihistamines to warrant
16 requiring such data which, as Dr. Ganley mentioned
17 earlier, would result in three years of exclusivity
18 for the manufacturer?

19 DR. BLEWITT: Well, I think of allergy as
20 a spectrum, and I think that there is a target
21 audience that will take first-generation
22 antihistamines and there has been a demonstrated
23 target audience for second-generation
24 antihistamines. What hasn't been demonstrated is
25 an appropriate target audience for

1 second-generation antihistamines OTC. I think
2 Schering Plough had worked that out very nicely in
3 that slide in which they compared the first and
4 second generation antihistamines and their
5 applications.

6 DR. BRASS: Well, I think what you have
7 highlighted is one of the many unusual aspects of
8 our consideration today. Nobody has told us
9 explicitly what the indication would be. Would it
10 be a take once and forget label, or would it be
11 take daily for the rest of your life label, or some
12 place in between? I think what has been suggested
13 by the agency is if it mapped through the existing
14 set of approved labeling indications, etc., then
15 there might not be as much concern. In contrast,
16 if it was mapping into a different set of use
17 domains, then we might have very different
18 questions, as we with the experience with some of
19 the GI drugs.

20 DR. BLEWITT: And, my point is simply that
21 that is a big unknown.

22 DR. BRASS: Dr. Johnson?

23 DR. JOHNSON: I think I am struggling too
24 a little bit with this concept that studies aren't
25 needed. One of the ways I am looking at it is if

1 this had been a sponsor-initiated request and they
2 came and said we don't need to do any studies; we
3 don't need actual use studies; we don't need label
4 comprehension studies; this is straightforward, my
5 suspicion is we would send them home and say we
6 disagree -- perhaps not --

7 DR. BRASS: You are so cynical!

8 DR. JOHNSON: So, I guess sort of related
9 to that -- I have not been on this committee long
10 enough to see second, third, fourth drugs in class
11 go OTC. Is it only the first drug in a class that
12 is required to do studies and everybody else can
13 just come and say I am an NSAID and, therefore, I
14 can go OTC?

15 DR. GANLEY: I think the important point
16 here is whether we believe the current OTC
17 monograph for antihistamines is relevant here, and
18 the previous drugs that have been switched from
19 prescription to OTC have taken on essentially the
20 same labeling. Now, with that given, any company
21 that would come in and ask us what they would be
22 required to do to switch, it would not include a
23 requirement for a label comprehension or an actual
24 use study. If they want to do one, that is fine.
25 The question is whether it is essential for a

1 supplement. It is not.

2 I have heard a lot of very carefully
3 worded statements today suggesting that somehow
4 this use as an antihistamine for allergic rhinitis
5 as second generation is somewhat different than
6 first generation, and I can't really figure that
7 out because if there is a concern about
8 self-diagnosis I think the issue becomes whether we
9 should actually revoke the OTC antihistamine
10 monograph. Because if people believe that people
11 cannot self-diagnose here, then we have a big
12 problem.

13 DR. JOHNSON: I have a very specific
14 question that really follows up to the lack of data
15 presented, and either industry or FDA can answer.
16 That really sort of goes to I think pharmacokinetic
17 and drug interaction questions. For loratadine,
18 one of the FDA slides said that it is metabolized
19 by 3A4 and 2D6, and I really don't have any idea
20 what the contribution of 2D6 is but, clearly, the
21 interaction studies you did, did not include a 2D6
22 inhibitor. So I am wondering is there data and you
23 just didn't tell us about that, or is the
24 contribution so minor that it wouldn't matter?

25 DR. MEYER: The contribution is minor.

1 DR. JOHNSON: Minor enough that you
2 probably don't list it as being a metabolizing
3 enzyme, an important metabolizing enzyme.

4 DR. MEYER: Yes, I did not focus on it
5 because that is a relatively minor pathway compared
6 to the 3A4, but the 3A4 data suggests that while
7 there is an increase in exposure to loratadine and
8 desloratadine that result from concomitant
9 administration, it is not very striking and doesn't
10 have important clinical consequences.

11 DR. JOHNSON: Okay, and cetirizine was
12 described as a renally eliminated drug, and based
13 on the information in the package insert I am
14 concluding that when you correct for protein
15 binding it is a drug that undergoes secretion. So,
16 I disagree with the assertion that there cannot be
17 drug interactions. Clearly, lots of drugs that do
18 have secretion drug interactions. So, I guess sort
19 of my big question relative to drug interactions is
20 based on high dose studies, overdose studies, the
21 drug interaction studies that have been done, do
22 you feel confident that even if there is some drug
23 interaction that is currently undiscovered that
24 would result in a 10-fold -- whatever, 15-fold
25 increase in concentration that would not pose any

1 problems in terms of arrhythmias or some event?

2 DR. MEYER: We don't have those data but I
3 feel confident from the data we have that it is
4 unlikely that anything is going to cause a 10- or
5 15-fold increase in exposure.

6 DR. BRASS: Dr. Vollmer?

7 DR. VOLLMER: I have three questions, two
8 of them directed to the FDA and one to industry.

9 DR. BRASS: Please try to keep them brief
10 questions.

11 DR. VOLLMER: Sure. The first one, in the
12 docket that we have received there was the mention
13 that there are some new products that contain these
14 compounds that are on the market that weren't
15 mentioned in the application or the original
16 petition but that would be considered as part of
17 any action that is taken. So my question is do we
18 have an option? Is it going to be feasible for us
19 to recommend that some formulations go forward as
20 OTC but others not. For instance, some of them are
21 recently developed formulations in pediatric
22 preparations which may need further evaluation, and
23 others are okay, or is it your sense that if we go
24 one step we go all the way with a given compound?

25 DR. MEYER: No, I think from our

1 standpoint you should not be taking your advice as
2 being all or none, either in terms of the overall
3 three drugs but even within the drugs the number of
4 indications, formulations and age range could all
5 be kind of ferreted out or spoken to separately in
6 your advice.

7 DR. VOLLMER: Thank you. The second
8 question, and bits and pieces of this have been
9 addressed with all your comments, there has been a
10 lot of suggestion that we are lacking data; we are
11 lacking actual use data perhaps. Granting your
12 contention that we don't need to do the label
13 recognition and the actual use studies, just from
14 the perspective of safety, is your perspective
15 that, given the FDA analysis, we have comparable
16 safety data and experience with these compounds as
17 we would in other situations where switch decisions
18 come up?

19 DR. MEYER: I think we presented the data
20 that we have available, and we are really seeking
21 advice from the committee that gets to the answer
22 of your question. I think it would be presumptuous
23 of me to answer that question considering the
24 questions we asked the committee.

25 DR. VOLLMER: Thank you. The final

1 question will be directed to industry. I am
2 interested, given that these products are available
3 in OTC formulations in other countries, have the
4 companies opposed these products going OTC in those
5 settings? If not, from a safety perspective, what
6 makes it important to oppose this here, in the
7 U.S., whereas it didn't make it important to oppose
8 it elsewhere?

9 DR. NADER: As far as fexofenadine is
10 concerned, fexofenadine is not available OTC
11 anywhere in the world. Fexofenadine is available
12 at Schedule 3 in Canada, Australia, New Zealand and
13 South Africa, and more recently actually we
14 submitted a request to the U.K. authority for a
15 Schedule 3 and it was rejected based on the fact
16 that they felt we did not submit enough data. And,
17 we don't have any intention to switch fexofenadine
18 to a real OTC status, which is the unscheduled
19 status, anywhere else in the world.

20 DR. SPIEGEL: I would echo that our record
21 is that everywhere in the world that we can seek
22 prescription status that has been our preference.
23 Only in those countries where we had no choice and
24 we were given a choice of not introducing the
25 product at all or introducing it as something less

1 than prescription have we gone that route.

2 DR. JENKINS: Dr. Brass, could I make a
3 clarification on the Canadian issue? We don't have
4 anyone from the Health Protection Branch in Canada
5 here today. We have consulted with them. I think
6 one clarification is needed on the status in
7 Canada, and that is a definitional one. You can
8 walk into a pharmacy in Canada and buy all three of
9 these products off the shelf without consulting
10 with the pharmacist. I think the expectation is
11 that a pharmacist is available in the store that
12 you can consult with if you choose, but there is no
13 requirement that you consult with a pharmacist. In
14 fact, I bought all three of these products last May
15 in Toronto. They are available on the shelf. You
16 do not have to consult a pharmacist.

17 DR. BRASS: Just to expand on that, is it
18 accurate to say they are not available in gas
19 stations?

20 DR. JENKINS: I don't know the answer to
21 that question but I think it would imply that they
22 are not.

23 DR. NADER: The only exception is if the
24 gas station has a pharmacist. Other than that, it
25 would be illegal, frankly, that the drugs would be

1 available. Again, we cannot control activities of
2 each pharmacist in Canada, but we believe that most
3 pharmacists follow what the rules and regulations
4 are and have product in a restricted area.

5 DR. BRASS: Thank you. Dr. Ford?

6 DR. FORD: Dr. Nader, in your presentation
7 you mentioned post-marketing labeling changes that
8 have had to be made, and I am wondering to what
9 extent you anticipate more of that coming and how
10 much it bears on the recommendations that we might
11 make with regard to safety today. And, please
12 comment, because you didn't elaborate on that in
13 your presentation about how serious those labeling
14 changes that had to be made were.

15 DR. NADER: Thank you for the question,
16 doctor. We counted that we had five labeling
17 changes since the drug was first introduced, back
18 in 1996. Now, I cannot comment on the fact whether
19 we could consider those changes as serious or not
20 but I could give a couple of examples, one of them
21 being in 1998, I believe. We revised the labeling
22 completely concerning the overdose. Again, most
23 recently -- I think it was approved just in
24 November, we revised completely -- not completely
25 but we revised a significant portion of our adverse

1 reactions section as it relates to our
2 post-marketing surveillance.

3 DR. BRASS: Dr. Uden?

4 DR. UDEN: For the FDA, I just want to get
5 the final piece of the puzzle of safety in my mind,
6 and this is my final piece, the adverse event
7 reporting system here does not include data from
8 foreign countries. What information do we have
9 from Europe, from Africa, from Australia and New
10 Zealand which supports or refutes the safety
11 information that you presented for the United
12 States?

13 DR. MEYER: I am going to let one of my
14 colleagues from the Office of Post-Marketing Drug
15 Risk Assessment answer that.

16 DR. TRONTELL: Anne Trontell. In fact, we
17 do obtain serious reports from foreign countries,
18 and those were considered in the analyses that were
19 presented today.

20 DR. BRASS: Dr. Wood?

21 DR. WOOD: I am still trying to agonize
22 over the safety issue. I need some help in
23 resolving the conflicting presentations that we
24 have heard. As I understand what we are being
25 told, the manufacturers have serious safety

1 concerns about the drugs but in response to Dr.
2 Roden's question, the response was that none of
3 these safety concerns were sufficiently severe to
4 have had them mount any specific study of any sort
5 going forward. Is that correct?

6 DR. NADER: I beg to differ on this one.
7 Again, once the drug is on the market we have a
8 very active post-marketing surveillance system that
9 is in place that tracks and follows up all adverse
10 events. We know that if the drug goes OTC we lose
11 about 70-80 percent of the number of adverse
12 events. We also know that the quality and the
13 quantity of adverse events changes. We also have
14 in our post-approval trials a very specific, very
15 rigid, very comprehensive section on safety. So,
16 in all our trials we collect safety data. When we
17 run a trial with 2000, 3000 or 4000 patients, when
18 these patients have to report any adverse event on
19 a case report form with the physician, I think this
20 improves and enhances our knowledge of the drug.
21 Actually, just as a simple example, our
22 post-marketing section within our label was mainly
23 derived from our post-approval trials.

24 DR. WOOD: I understand what the
25 regulations say about looking for adverse events in

1 clinical trials. My question again to you is give
2 me an example of a specific safety concern that you
3 are currently pursuing, that you are sufficiently
4 concerned about to have mounted a study with a
5 hypothesis that says this is a real concern to us
6 and we are pursuing it right now, and that is why
7 we don't think it should go over-the-counter.

8 DR. NADER: The answer to this question is
9 very simple. The answer to this question is we
10 need to carefully monitor the adverse events that
11 are in our current label and make sure that we
12 capture, through clinical trials and through active
13 post-marketing surveillance, any signal. We need
14 to make sure that we analyze the signal. We need
15 to make sure that we derive data.

16 To tell you that we picked up a signal and
17 we are running specifically a trial to confirm the
18 signal is simply not happening. We are not running
19 a specific trial just to confirm a signal, but we
20 are continuing to collect information in a very,
21 very diligent way.

22 DR. WOOD: No, but to help me resolve my
23 problem, what I am hearing you say -- I just want
24 to make sure that we have got this right -- is that
25 you have not identified a specific safety concern

1 right now that has made you want to pursue that
2 more vigorously. You just want to keep collecting
3 more data in an untargeted fashion in the hope of
4 picking something up. Is that correct?

5 DR. NADER: With your permission, I would
6 like to defer this question to the head of our
7 global pharmaco-vigilance who could address it more
8 specifically.

9 DR. LEGERIN: We are continuously
10 monitoring a number of issues, some of which were
11 highlighted by the FDA's analysis as well. On some
12 of the topics, we overall agree with their analysis
13 of the post-marketing safety data. What I would
14 like to show you, if you would put the slide on
15 please, is what happens when the product goes
16 over-the-counter.

17 [Slide]

18 This is ranitidine with post-marketing
19 surveillance adverse event reports, indicated in
20 the pink line there, coupled with how many days of
21 patient exposure. You see where the OTC switch
22 occurred, roughly around 1996, and you see a
23 precipitous plummet in the number of adverse event
24 reports despite the fact that the exposure remains
25 at least as high. In fact, this is IMS data which,

1 once the product goes OTC, grossly underestimates
2 the patient exposure. So, what we see now is high
3 patient exposure, low volume of adverse event
4 reporting. You effectively lose your ability to
5 monitor the products.

6 We feel that the safety profile of
7 fexofenadine, as we currently know it under the
8 prescription status, is a good profile, and we do
9 have some issues, as I said, similar to what the
10 FDA has highlighted, that we continue to monitor.
11 Our concern is that the product has been on the
12 market four and a half years, and some of the newer
13 and higher dose formulations only for a year, and
14 that is just not sufficient time, based on what we
15 know historically, for us to feel confident that we
16 know everything about the drug, and that we have
17 uncovered it, and that we will have sufficient
18 opportunity to be able to uncover those kinds of
19 things in the future if we are put into an OTC
20 situation where we essentially can't effectively
21 monitor the product.

22 DR. WOOD: I think that is helpful because
23 I think it tells us that none of these issues are
24 sufficiently important that they have required
25 specific action on the company's part.

1 DR. D'AGOSTINO: That is a very profound
2 statement, but wouldn't that be the case with
3 almost all drugs that are prescription? I mean, if
4 something pops up you look for it but, I mean,
5 don't you wait for things? I think there is sort
6 of a glibness in the way you are stating that that
7 maybe you don't mean.

8 DR. WOOD: If you look at the history, and
9 somebody touched on that earlier -- if you look at
10 the history of drugs which have had significant
11 problems, in the period that preceded the problem
12 being finally nailed down there were studies under
13 way that were trying to work on that, that were
14 examining that, that were trying to work out
15 mechanism and sometimes discount the existence of
16 the problem. So, there is a pattern that usually
17 --

18 DR. D'AGOSTINO: And we are saying we
19 think the period is long enough for those not to
20 have appeared yet or to appear.

21 DR. WOOD: Well, with fexofenadine, as we
22 have heard two or three times now, the active
23 molecule has been on the market for an
24 extraordinarily long period of time --
25 extraordinarily long period of time.

1 DR. BRASS: Dr. Barainuk?

2 DR. BARAINUK: I think we have to inject
3 some physiology into this. Since the FDA docket of
4 25 years ago, we have learned a lot about the
5 pathophysiology and it is clear that the early
6 symptoms of allergic rhinitis, antigen-induced
7 symptoms would be due to histamine release --
8 itchy, watery, runny eyes and nose. That is what
9 this class of drugs is designed to block. The late
10 phase, the more chronic phase of inflammation
11 though, the reason that people find that their
12 antihistamine stopped working is the inflammatory
13 cascade, the TH2 lymphocyte eosinophil
14 inflammation. I think it is important for everyone
15 here to recognize that the antihistamines do
16 absolutely nothing for that part, and that the
17 antihistamines at that point would fail and that
18 should trigger a visit to a doctor.

19 Dr. Ganley opened this whole can of worms
20 about should we go back and reevaluate all the
21 over-the-counter antihistamines.

22 DR. BRASS: I closed it again.

23 [Laughter]

24 DR. BARAINUK: I just want to make one
25 point, and that is that those drugs, as was

1 mentioned earlier, about 50 percent of the drug use
2 is for the common cold. So, if these drugs go
3 over-the-counter, is that likely to be their
4 primary indication rather than the itch and the
5 drip of allergic rhinitis? That is my contention,
6 that is what would happen.

7 I would like to ask the representatives
8 from our sponsor, Dr. Seidman, someone from Blue
9 Cross/Blue Shield, as a representative of this
10 exemplary healthcare system, have you done any
11 studies on intermittent and persistent rhinitis
12 with the three drugs in question?

13 DR. SEIDMAN: No, we have not committed
14 any studies on that subject.

15 DR. BARAINUK: And, have you done a study
16 on patient self-diagnosis of allergic rhinitis?

17 DR. SEIDMAN: No, we have not.

18 DR. BARAINUK: And, have you done a study
19 of patient self-treatment?

20 DR. SEIDMAN: Again, the answer is no
21 because we based our petition on the old version of
22 the FDA monograph, that it has been established
23 that patients can readily diagnose and treat
24 allergic rhinitis.

25 DR. BARAINUK: And, not on current

1 physiological parameters and current practice
2 guidelines?

3 DR. SEIDMAN: No. The answer would be no.

4 DR. BARAINUK: So, are you developing a
5 program to facilitate patient self-management using
6 over-the-counter products alone?

7 DR. SEIDMAN: I am sorry, the rationale
8 for our petition was to bring to the attention of
9 the Food and Drug Administration what we believe to
10 be an inconsistency in the marketing of these
11 products and the fact that, based on the FDA
12 monographs, allowing access to the
13 second-generation antihistamines would be
14 beneficial to allergy sufferers. We have not
15 participated in any specific clinical trials or
16 investigations.

17 DR. BARAINUK: So that the current plan of
18 having a patient see a doctor, get an organized
19 plan of allergen avoidance, of antihistamine use
20 where necessary, of nasal steroids and other
21 treatments as required, that is not considered to
22 be a cost effective way of taking care of this
23 problem?

24 DR. SEIDMAN: Oh no, not at all. We are
25 encouraging patients to see physicians. The issue

1 here is does the drug modality have to be a
2 prescription drug.

3 DR. WOOD: While you are up there, as the
4 rationale in this petition was to get more access
5 to the drugs, presumably you are going to pay for
6 these drugs? Is that correct? You are planning to
7 change your plan to pay for the drugs that they are
8 going to obtain to ensure that they get this
9 increased access? Am I correct in that?

10 DR. BRASS: Again, you do not need to
11 answer that rhetorical question if you don't want
12 to. If you would like to, please feel free.

13 DR. SEIDMAN: I can answer the question.
14 I am chief pharmacy officer for WellPoint Health
15 Networks. We have ten million members that we are
16 responsible for. We have prescription drug trends
17 that are increasing at over 15 percent per year.
18 We have a responsibility to our individuals who are
19 purchasing insurance, to the employers who are
20 purchasing insurance to provide broad access to an
21 affordable pharmacy benefit.

22 We believe that these drugs are incredibly
23 safe and as effective as the first-generation
24 antihistamines. As such, they should be available
25 in an over-the-counter environment, and patients

1 should be able to access them just as they are
2 accessing the first-generation antihistamines
3 today.

4 We filed the petition to the agency so
5 that you would convene a panel of experts, as we
6 have today, to wrestle with these particular
7 issues.

8 DR. BRASS: Dr. Gilliam?

9 DR. GILLIAM: FDA, in your executive
10 summary you talk about that there is a causal
11 relationship between Claritin and seizures in 26 of
12 the 43 seizure cases, and then say in 17 of 30
13 cases with fexofenadine there were new onset
14 seizures. But then in your presentation you said
15 there was not any relationship in any of the drugs.
16 I just want to make sure.

17 DR. MEYER: It is rather that causal
18 relationship could not be excluded in those cases.
19 Post-marketing data can rarely, if ever, in and of
20 itself give you a causal link.

21 DR. APTER: We have had a lot of
22 information about safety today in patients who have
23 equal access to the medication and we have talked
24 about access. What concerns me about today is what
25 we are effectively doing one way or another is

1 shifting the access to these medications for
2 patients.

3 Now, currently, patients who are in the
4 lowest socioeconomic category probably have access
5 to these medications. If we shift and make them
6 over the counter, they will lose access. In
7 another group that probably didn't have access,
8 people with very limited resources but not on
9 public assistance for healthcare will lose access.
10 In this very partitioned discussion about safety
11 today, in this committee, we ignored that a bit,
12 although it has been talked about. I am wondering,
13 addressing the FDA in the way this discussion is
14 partitioned, what we can do about these health
15 disparities, in effect, based on the socioeconomic
16 position of patients.

17 DR. BRASS: Before anybody answers, let me
18 emphasize there are some assumptions built into
19 this which have not been challenged that, in fact,
20 for the indigent, the largest barrier to accessing
21 a product may be the cost, tangible and
22 intangible, to getting to a physician, as compared
23 to accessing a drug in another setting.

24 DR. APTER: Right, but once they get to
25 the physician, and many formularies do cover these

1 drugs --

2 DR. BRASS: All I am saying is that, in
3 terms of the data that quantifies these disparities
4 and barriers, there are a lot of things being said
5 which I do not think are uniformly supported by
6 data in terms of the magnitude of the barriers and
7 their relative impact on diverse populations.

8 DR. APTER: Well, I am not sure, but --

9 DR. GANLEY: Let me just point out that,
10 in almost every situation of a prescription-to-OTC
11 switch, you are going to have the same situation
12 where the cost is greater in the prescription. The
13 thing that brings cost down is competition,
14 generally the generic competition will bring it
15 down.

16 But, if we start basing decisions on
17 whether something should be OTC because of the
18 issue that you raised, nothing will ever get taken
19 to over the counter. Just think about it. Every
20 prescription, if it is covered by a health insurer
21 and you want to go OTC and it doesn't become
22 covered, that situation applies to everything we
23 review.

24 It applies to the cholesterol-lowering
25 agents that we talked about last year, or to the

1 proton-pump inhibitors, every situation. So, if we
2 start taking that into account, nothing will ever
3 go OTC. You can forget about self-care.

4 DR. MEYER: More importantly, I would
5 point out that, as a big fan of Hubert Humphrey, I
6 don't know how he would have regarded today's
7 meeting and I wouldn't be so presumptuous to guess,
8 but I would say that it is not a part of the
9 Humphrey-Durham Amendments.

10 Granted, that was some time ago, but, as
11 the Humphrey-Durham Amendment and the Food, Drug
12 and Cosmetic Act currently is written,
13 consideration of cost is not what part of what
14 makes the drug Rx versus what makes it OTC.

15 DR. APTER: I understand that. I just
16 wanted to raise the point that there is something
17 beyond this committee that needs to be considered.

18 DR. BRASS: It may be more than one thing.

19 DR. JOAD: This is regard to sedation and
20 for Dr. Meyer. The approved first-generation
21 antihistamines have a fair amount of sedation. We
22 are considering some sedation in the second-
23 generation ones. Should we assume that because the
24 monographs and the new drug applications for the
25 first-generation approved that amount of sedation

1 that, then, that would be also acceptable for the
2 second-generation?

3 Or are we just looking at safety
4 completely separate from those first-generation FDA
5 --

6 DR. MEYER: I think you can take into
7 account the factors you would like to take into
8 account. I think one of the questions, should the
9 recommendation of committee be affirmative, is
10 about issues that might be mentioned in the
11 labeling, including sedation. But, again, I think
12 you take into account what you take into account.

13 DR. BRASS: I would like to ask a couple
14 of questions, myself, primarily, I think, to the
15 FDA. But if either of the manufacturers have
16 information on this, I would be interested.

17 This goes to the issue of special
18 populations and drug interactions. The materials
19 provided as data, and sometimes not as data but
20 only alluded to a variety of circumstances where
21 the area under the curve for the drug concentration
22 in plasma changed substantially; the elderly for
23 loratidine, a number of drug interactions where
24 mean changes were 50 percent, which means, for some
25 patients, they were probably 100 percent changes.

1 In the case of cetirizine and loratidine,
2 we also heard that the degree of somnolence appears
3 to be dose-related. Yet, we also heard that none
4 of these effects were felt to be clinically
5 significant as your conclusion.

6 I was wondering on what confidence you
7 concluded that a 50 percent increase in the area
8 under the curve would not result in a clinically
9 significant change in somnolence.

10 DR. MEYER: I, perhaps, should have been
11 more explicit on that point. I did not mean to
12 exclude the fact that sedation might be more common
13 with drug interactions. What I meant to speak to
14 is really significant cardiac effects or other
15 untoward effects beyond what might be
16 pharmacologically predicable.

17 DR. BRASS: Again, in assessing whether
18 labeling can adequately inform the consumer as to
19 potential risks and how they should be avoided,
20 those situations become important. Can you
21 summarize, or anybody just summarize, for us the
22 conditions, either in special populations or drug
23 interactions with area-under-the-curve changes of
24 50 percent or more, compared to a healthy, young
25 population have been identified.

1 I said I saw elderly for loratidine. Does
2 anybody have a summation of those conditions which
3 might represent special considerations?

4 DR. MEYER: For loratidine, it was hepatic
5 impairment. Actually, I should open up the
6 labeling, but it was hepatic impairment and renal
7 impairment where there is a dosage adjustment, I
8 believe. For cetirizine, there is a dosage
9 adjustment.

10 Actually, what it is is a recommendation
11 towards the lower end of the dose scale for the
12 renally impaired and the hepatically impaired.

13 DR. BRASS: Were any of the drug
14 interactions associated with an increase of AUC of
15 more than 50 percent? Can anybody refresh my
16 memory about that?

17 DR. LORBER: I am Dr. Lorber from
18 Schering. In some of the interaction studies,
19 there were increases in AUC up to 300 percent.

20 DR. BRASS: Which were those; can you
21 remind us?

22 DR. LORBER: That was with ketoconazole.
23 In those studies, interestingly enough--they were
24 crossover studies, 24 patients in the crossover
25 study. As was mentioned, there was no evidence of

1 any untoward cardiac effects, no changes in
2 electrocardiograms, no changes in any of the ECG
3 parameters, QTC, et cetera.

4 I think it was also interesting to note in
5 those studies, although a small number of patients,
6 there actually was no increase in sedation even at
7 a 300-fold increase in AUC.

8 DR. BRASS: Similarly, I think it was
9 loratidine where taking with antacids decreased the
10 AUC; again, you concluded that that would not
11 decrease the effectiveness of simultaneous
12 ingestion?

13 DR. LORBER: I am not aware of that.
14 Perhaps you were thinking of cetirizine with
15 antacids.

16 DR. BRASS: Maybe I am misquoting. I
17 thought it was one of the materials where there was
18 a drug interaction.

19 DR. MEYER: I am not aware of any with
20 antacids. There are some minor food effects with
21 cetirizine and fexofenadine, but they are not of
22 major consequence, for the most part.

23 DR. MERINO: The Maalox, or the antacid
24 interaction you were referring to happens to be
25 with fexofenadine and there was about a 48 percent

1 decrease in the AUCs there. Our experience with
2 some of the other drug interactions, since your
3 question was a little bit open, is actually
4 somewhat similar to what we have seen with
5 loratidine.

6 Some of the more potent inhibitors such as
7 ketokonazole, you do see 2.0-fold, 2.5-fold, types
8 of increases in AUCs.

9 DR. BRASS: Again, the point is, in terms
10 of trying to label the product, would a decrease of
11 50 percent in the AUC be anticipated to decrease
12 the effectiveness of a dose of cetirizine?

13 DR. MERINO: It could.

14 DR. BRASS: Finally, to the FDA, one of
15 the things that just leaps out as being quite
16 different than everything we have talked about is
17 the thrombocytopenia issue with cetirizine. Could
18 you give us a bottom line as to your best estimate
19 as to potential frequency, its reversibility if
20 drug is discontinued, what would happen to those
21 people?

22 Again, it stands out so strikingly as a
23 potential differential adverse effect.

24 DR. MEYER: I am going to make a comment
25 and then, perhaps, one of my colleagues from OPMRA

1 would like to follow up. But I would say that I
2 did spend a little time talking about it in my
3 presentation because it does sort of show up, in a
4 manner, on the top-ten list that it doesn't on the
5 others.

6 But there are reports for the other
7 antihistamines and it is a fairly common adverse-
8 event term--well, relatively common adverse-event
9 term, I would say. But I think that there were a
10 large number of cases. When they were sort of
11 dissected out, they actually looked like they were
12 plausibly, potentially, causally related to the
13 cetirizine exposure.

14 It is in the labeling as something seen in
15 the postmarketing arena. It does not seem, then,
16 if you kind of tease out the cases, to be a very
17 strong signal. But it did catch our eyes as well.

18 DR. BRASS: Were those cases reversible?

19 DR. MEYER: I am going to defer.

20 DR. BRASS: Are there any rechallenge
21 cases in that list? Please, don't read the whole
22 list.

23 DR. WEAVER: I didn't do the review for
24 that. As I said, we started out with a bunch of
25 cases, over 150. Many of them turned out to be

1 fairly implausible because it wasn't even possible
2 to identify the case as a unique case. We had a
3 large group of cases where the individual case
4 couldn't actually be identified because it looked
5 like it was just a bunch of stuff from the Internet
6 that actually couldn't be confirmed.

7 In terms of outcomes, we did have one
8 death in that series and we had a case where the
9 count was lower than 1000. In terms of
10 rechallenge, I am not remembering that offhand. I
11 will check, if you would like me to do that.

12 DR. BRASS: Thank you.

13 **Final Questions**

14 I think, because of the time, to move the
15 process forward, I am going to ask that we proceed
16 to the questions that have been posed to us by the
17 FDA which will add some additional discussion
18 amongst ourselves but in a much more focused way.

19 This is also my chance to completely
20 inadequately attempt to explain the intent of the
21 questions in a way that decreases our confusion and
22 focusses our device. In five years, I have not yet
23 been successful, but I am not going to stop trying.

24 The questions we have been posed may
25 appear to be very broad, broad in the sense that

1 they require information, much of which we have
2 discussed, which we really don't have. They all
3 are of the form, "Does drug X have a safety profile
4 acceptable for OTC, marketing; i.e., can it be used
5 safely without a learned intermediary?"

6 I am going to ask you to answer the
7 question initially with the following assumptions;
8 that any dose that has been marketed meets this
9 criteria; that any product containing the drug
10 under discussion meets the standard -- i.e., you
11 can consider single-ingredient products or multi,
12 whatever you want to consider -- in any population.

13 So, if there is a subpopulation where you
14 do not think the answer is yes, you can still
15 answer the question yes and clarify it later with
16 any conceivable labeling. If you think the safe
17 use requires warnings, et cetera, on the label,
18 still answer yes and you will have an opportunity
19 to specify what clarifications you would like on
20 the label.

21 Only use the data to which we have access.
22 You cannot imagine another set of data. You can
23 only use what has been presented. If, based on
24 that, you cannot answer the question to the
25 affirmative under any circumstance for any

1 population with any label that you think is
2 reasonable, then you would answer the question no.

3 How bad did I do?

4 DR. RODEN: You assumed anybody pays
5 attention to the label, to start with.

6 DR. BRASS: Oh; I thought you were going
7 to say anybody pays attention to me.

8 So, the first question that we will
9 discuss in that framework is, "Does loratidine have
10 a safety profile acceptable for OTC marketing;
11 i.e., can it be used safely without a learned
12 intermediary?"

13 In response to Dr. Roden's comment, if you
14 think that there is a warning or a label
15 requirement that would be so absolute that, if it
16 were ignored, would represent public safety, then
17 you could not vote yes on the available data, would
18 how be I would respond to your query.

19 That question is open for discussion.

20 DR. VOLLMER: Can I make sure that I
21 understand that, then? So, even if we put a
22 warning label on there, if our feeling is, were
23 that ignored, it poses a substantive public-health
24 risk, we would vote no?

25 DR. BRASS: That's correct. That would be

1 based on either the failure to have data that it
2 would be heeded--i.e., a label-comprehension
3 actual-use study--or its dissimilarity to other
4 similar labels that are on use; for example, the
5 existing products have a drowsiness warning and so
6 if, by analogy, that was the only warning that was
7 required, one might reasonably assume that that
8 would support a yes.

9 DR. BARAINUK: What is the indication,
10 again? Just to be specific for this, is this going
11 to be intermittent use for seasonal allergic
12 rhinitis and not an indication for common cold as
13 some of the other drugs have, the first-generation
14 drugs?

15 DR. BRASS: That is correct. Again, if
16 you feel a refinement is necessary, a further
17 refinement, and you feel that refinement differs
18 substantially from language that has been consumer-
19 tested, you might consider a no vote requiring
20 evaluation of the new indication.

21 If the indication you are supporting in a
22 yes vote is one that the agency has previously
23 included in monograph form, then the extrapolation
24 might be reasonable. But, again, the question is
25 open-ended on purpose.

1 DR. BARAINUK: So, should the indication
2 be limited to those symptoms that are known to be
3 amenable to treatment with each of these three
4 drugs?

5 DR. MEYER: I just wanted to clarify one
6 thing and that is about the common cold. In fact,
7 the OTC single-ingredient antihistamines, other
8 than Tavist which did specific studies, do not have
9 the indication of the common cold.

10 Obviously, the combination products often
11 are given the name "cold" because of the
12 decongestant properties. But I think you could
13 probably use the labeling, or even the suggested
14 labeling from Blue Cross/Blue Shield as sort of the
15 framework for what type of indication you might
16 imagine you are speaking to right now, which is for
17 the chlorpheniramine product, is, "temporarily
18 relieves these symptoms due to hay fever and other
19 upper respiratory allergies, sneezing, runny nose,
20 itchy eyes, itchy, watery throat."

21 DR. BRASS: Dr. Fink?

22 DR. FINK: I will take a stab at it voting
23 yes with a generic comment that it strikes me--

24 DR. BRASS: We are not voting. We are
25 discussing. You may discuss.

1 DR. FINK: I guess, at this point, my
2 comment for discussion is I think, if there are not
3 safety concerns, and I have not heard any this
4 afternoon, I think that there is a general issue
5 that OTC monitoring needs to be improved because,
6 obviously, any drug that is OTC can have an drug
7 interaction with a newly developed class of drugs
8 that is approved for prescription use.

9 So, I am concerned that the OTC
10 monitoring, in general, maybe needs to be improved.
11 But I do not see any reason that the drugs under
12 discussion today have any reason to have concerns
13 about their safety for OTC use.

14 DR. BRASS: Dr. Roden?

15 DR. RODEN: I just wanted to clarify the
16 indications issue. I went to my magnifying glass
17 and I think I read the indications for the three
18 drugs. I know you are trying to focus on one, but
19 they are somewhat different. Seasonable rhinitis
20 and urticaria for the first two, and then this
21 perennial allergic rhinitis for Zyrtec. I am just
22 trying to clarify the fact that we are mixing
23 apples and oranges a little bit.

24 And then there is this urticaria issue
25 which we haven't talked about, but it is my sense

1 that when we touched on it, most people thought
2 that that was not part of the Blue Cross petition
3 and not part of your agenda. Is that a fair thing
4 to say?

5 DR. MEYER: I think that is a fair
6 statement. The absolute distinction between
7 perennial and seasonal allergic rhinitis which we
8 apply to prescription marketing has not been made
9 in the OTC setting. The wording of the OTC
10 antihistamines does speak to temporary use, but it
11 mentions hay fever and other respiratory allergies.

12 DR. RODEN: I guess I have it here. A
13 reasonable label might say, "If you use it for more
14 than a week and don't get better, go see your
15 doctor," or something like that. I will find it
16 eventually.

17 DR. MEYER: That is actually a very common
18 type of wording in the OTC labeling.

19 DR. BRASS: But I notice that, in fact,
20 and you can correct me if I am wrong, that the
21 existing antihistamine monograph does not have such
22 language. It does not have language about fever or
23 other cues that might indicate a process other than
24 allergic rhinitis as an indicator.

25 Is there a history behind the absence of

1 that, what I agree is very typical language in the
2 OTC setting, from the antihistamine monograph?

3 DR. GANLEY: I would have to refer back to
4 the panel report and that issue never came up.
5 Certainly, one of the issues, and it is a resource
6 issue, is to update these monographs and to try to
7 improve the language of labels. So that is
8 potentially an issue if we thought there was a
9 problem out there with that.

10 Dr. Dykewicz.

11 DR. DYKEWICZ: In fact, that is one of my
12 problems right here. I don't think I am having so
13 much problem with some of the safety issues with
14 these particular drugs, but I am really almost to
15 the point of grave concern about the simplicity of
16 the monograph, which I know is simple for a reason.
17 You want to have, for a consumer product, something
18 that is easily understood that could provide some
19 good guidance to the consumer.

20 On the other hand, I think the distinction
21 between seasonal allergic rhinitis and perennial
22 allergic rhinitis is very important and that is
23 because of the ability of the consumer to self-
24 diagnose.

25 It is one thing for an individual to be

1 able to say, "Yeah; every year during the ragweed
2 season, I have itchy, watery, runny eyes and a
3 stuffy, runny nose." It is quite another thing to
4 have a stuffy nose on a year-around basis and to be
5 able to assess whether that is perennial
6 nonallergic rhinitis, which I think a lot of
7 consumers don't even know exists, and perennial
8 allergic rhinitis, let alone other issues of
9 presence of nasal polyps and that sort of thing.

10 So I think the monograph, frankly, for all
11 the antihistamines, needs to be vastly improved
12 because we need several phrases in there that
13 really make the point that there can be, with more
14 prolonged problems, with the more prolonged
15 symptoms, nonallergic nose problems and that you
16 should seek the advice of medical care for those
17 sorts of situations.

18 DR. MEYER: Advice noted.

19 DR. BRASS: Dr. Johnson?

20 DR. JOHNSON: In the sample label that you
21 gave us, is this a real chlorpheniramine label, or
22 is it a sample chlorpheniramine label? The reason
23 I am asking is that, the way I read it, it doesn't
24 say temporary use. It says that it temporarily
25 relieves, blah, blah, blah.

1 So I don't read anywhere in here a
2 limitation on the time people are supposed to use
3 this product.

4 DR. GANLEY: There is no limitation. So
5 if someone is comfortable with taking an over-the-
6 counter antihistamine and has to use it on a
7 regular basis, there was no recommendation that
8 there should be a limitation on it.

9 DR. BRASS: Dr. D'Agostino?

10 DR. D'AGOSTINO: The last few questions,
11 actually, are very much what I was going to ask.
12 But I want to go back to the safety data. These
13 drugs are still under NDAs and so forth, so if the
14 switch happens, if we recommend a switch, the
15 intensity of the follow up that is normal doesn't
16 suddenly drop; right?

17 So we are not, by saying it is an OTC,
18 suddenly saying that we aren't worried about
19 potential safety things coming up and what have you
20 and new signals popping up.

21 The other is the safety of the temporary
22 use that I battled with a couple of times. One of
23 the drafts has prolonged use should only be done
24 with the advice of a physician, but it just was
25 mentioned this temporary relief means you could go

1 on chronically. What is supposed to be the case
2 with these drugs? Is it chronic use is possible as
3 a temporary relief?

4 DR. GANLEY: Yes; under the monograph,
5 chronic use is permitted.

6 DR. D'AGOSTINO: It is permitted.

7 DR. GANLEY: It is permitted. That was
8 based on the data that was presented to the FDA and
9 the panel looking at that. That was what was
10 decided on.

11 DR. D'AGOSTINO: And a lot of the usage is
12 presumably, even with the first-generation, chronic
13 use.

14 DR. GANLEY: Right. I think it is very
15 interesting, though, these issues being brought up
16 today by the sponsors regarding the ability to
17 self-determine whether you have this condition, two
18 of these three companies market drugs under the
19 monograph and this issue was never brought up to us
20 before.

21 This petition has been sitting out there
22 since 1998. Only one of the companies submitted a
23 response to it, a one-page response, saying that
24 they disagreed. There was no data presented to it.

25 So it is very interesting how all these

1 issues sort of--and I am actually glad we had this
2 meeting because they have brought these issues to
3 light that we actually may have to look into a
4 little bit further.

5 DR. BRASS: My issue with the chronic use
6 is not that it may be used chronically, but to help
7 the consumer who does not get relief understand and
8 have realistic expectations, that the percentage of
9 consumers who will get relief will not be 100
10 percent and that to expect that would be
11 unrealistic, or to lead a consumer to believe that
12 they should continue to take it for a longer period
13 and not have a clear expectation, and to help cue
14 the lack of response, not to flag a potential risk.

15 DR. D'AGOSTINO: This prolonged usage that
16 was in one of the recommendations I think is
17 something we wanted to go back to.

18 DR. MEYER: I just wanted to reemphasize
19 the point about the chronic use, that two of the
20 three agents under discussion today actually are
21 specifically indicated for seasonal allergic
22 rhinitis which would, presumably, be less chronic
23 in use because it is an episodic condition.

24 I don't think we can make too much out of
25 what the average prescription is because most

1 health plans, I assume, are like mine. What I get
2 when I go to the pharmacy is a month's supply, or
3 as much as they are willing to pay for. How I use
4 it may be quite different.

5 DR. RODEN: A point of clarification. If
6 it is off the subject, I am sure Eric will tell me
7 that it is off the subject. If we were to say to
8 the agency that these drugs are appropriate for OTC
9 use, does that mandate the fact that they would go
10 OTC?

11 Is the sponsor under any obligation to
12 take a compound OTC? Do you have the power to say
13 it is OTC or nothing? Can't the sponsor turn
14 around and say, "Well, you know, that is very
15 interesting. But we don't want to market it in the
16 grocery store. We want to market it through
17 doctors."

18 DR. BRASS: Contrary to one of the slides
19 where somebody said the panel can decide, the panel
20 can't decide anything.

21 DR. RODEN: No; I know. Panel advisors.

22 DR. BRASS: So what the FDA does or
23 doesn't do with that advice and what their
24 regulatory position will or won't be--

25 DR. RODEN: My question is what

1 regulatory--do you have regulatory authority to
2 insist that something go OTC? That is just a point
3 of interest or clarification.

4 DR. MEYER: I am going to give you the
5 same answer that I have given members of the press
6 which is, "We are here today to seek your
7 scientific input on the science of this."

8 DR. RODEN: I guess you are running for
9 office.

10 DR. GANLEY: I think there are two issues
11 here. One is the scientific issues and the other
12 is the regulatory and legal issues. There are a
13 lot of lawyers in this audience that are going to
14 help us figure that out, I'm sure. So I think the
15 thing that we need to struggle with today is really
16 the scientific part of it and then whatever your
17 decision is, whether it is yes or no, we have to
18 handle the regulatory part.

19 DR. MEYER: And the ethics rules in the
20 Executive Branch prevent me from running for
21 office.

22 DR. BRASS: Can somebody summarize for me
23 the experience with loratidine in patients under
24 twelve years old, under six years old and under
25 two years old so we can get a better insight into

1 the degree the existing safety base extrapolates to
2 those populations?

3 Again, the issue of the amount of exposure
4 is critical implicitly in assessing the safety
5 profile, so that if 99.9 percent of the database is
6 derived from people over twelve, extrapolating that
7 to the pediatric population becomes potentially
8 less sound.

9 Can somebody clarify that for me?

10 DR. MEYER: I will, perhaps, let the
11 individual sponsors--I guess maybe I will need to
12 answer on behalf of Pfizer, but--

13 DR. BRASS: Let's pretend we are talking
14 about loratidine. So let's try to keep focused.
15 So, for loratidine, what is the pediatric--

16 DR. MEYER: I will let them speak to it,
17 but I did want to make the point that we have asked
18 for pediatric studies for such agents down to age
19 six months, in general, not because we necessarily
20 think the disease exists there but because we
21 understand that there is use of antihistamine
22 products down to that age range.

23 So we have asked for data broadly under
24 the pediatric initiatives for that. But I will let
25 the company speak to the specifics of the timing