



U.S. Food and Drug Administration

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

13 JUNE 30, 2009

14 8:00 a.m.  
15  
16

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P R O C E E D I N G S

- - - - -

DR. NELSON: Okay. If we could all take  
our seats, we can get started.

Thank you and welcome back to the second  
day of our meeting, our joint meeting of the three  
advisory committees on the issue of acetaminophen

1 and hepatotoxicity.

2 I'm going to read the opening remarks.

3 For topics such as those being discussed  
4 at today's meeting, there are often a variety of  
5 opinions, some of which are quite strongly held.  
6 Our goal is that today's meeting will be a fair  
7 and open forum for discussion of these issues and  
8 that individuals can express their views without  
9 interruption. Thus, as a gentle reminder,  
10 individuals will be allowed to speak into the  
11 record only if recognized by the chair.

12 In the spirit of the Federal Advisory  
13 Committee Act and the Government in the Sunshine  
14 Act, we ask that the advisory committee members  
15 take care that any conversations about today's  
16 topic take place in the open forum of the meeting,  
17 not during breaks, lunch or, for this meeting,  
18 overnight -- which was last night.

19 We are also aware that members of the  
20 media are anxious to speak with the FDA about  
21 these proceedings; however, like the advisory  
22 committee members, FDA will refrain from  
23 discussing the details of this meeting with the  
24 media until its conclusion. For the convenience  
25 of the media representatives, I would like to  
26 identify the press contact, Ms. Riley -- is she  
27 here? -- she was yesterday. If you're present,  
28 please stand.

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

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

7                   Elaine.

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

21                  The following information on the status  
22                  of this committee's compliance with federal ethics  
23                  and conflict of interest laws covered by, but not  
24                  limited to, those found at 18 USC section 208 and  
25                  section 712 of the Federal Food, Drug and Cosmetic  
26                  Act (FD&C Act) is being provided to participants  
27                  in today's meeting and to the public.

28                  FDA has determined that members and

1 temporary voting members of these committees are  
2 in compliance with federal ethics and conflict of  
3 interest laws under 18 USC section 208(b)(3).

4 Congress has authorized FDA to grant  
5 waivers to special government employees who have  
6 potential financial conflicts when it is  
7 determined that the agency's need for a particular  
8 individual's service outweighs his or her  
9 potential financial conflict of interest.

10 Under USC 208 (b)(1), Congress has  
11 authorized FDA to grant waivers to regular  
12 government employees who have potential financial  
13 conflicts when it is determined that the financial  
14 interest is not so substantial to be likely to  
15 affect the integrity of the individual's service  
16 to the government.

17 Under section 712 of the FD&C Act,  
18 Congress has authorized FDA to grant waivers to  
19 special and regular government employees with  
20 potential financial conflicts when necessary to  
21 afford the committee essential expertise.

22 Related to discussions of today's  
23 meeting, members and temporary voting members of  
24 the committees who are special and regular  
25 government employees have been screened for  
26 potential financial conflicts of interest of their  
27 own, as well as those imputed to them, including  
28 those of their spouses or minor children and, for

1 purposes of 18 USC section 208, their employers.

2 These interests may include investments,  
3 consulting, expert witness testimony, contracts,  
4 grants, CRADAs, teachings, speaking, writing,  
5 patents, royalties and primary employment.

6 For today's agenda, the committees will  
7 discuss and make recommendations regarding how to  
8 address the public health concern of liver injury  
9 related to the use of acetaminophen in both  
10 over-the-counter (OTC) and prescription (Rx)  
11 products.

12 This is a particular matters meeting  
13 during which general issues will be discussed.

14 Based on the agenda and all financial  
15 interests reported by the members and temporary  
16 voting members of the committee, it has been  
17 determined that all interest in firms regulated by  
18 the Center for Drug Evaluation and Research  
19 present no potential for a conflict of interest.

20 With respect to the FDA's invited  
21 industry representatives, we would like to  
22 disclose that Dr. Lorna Totman and Dr. Charles  
23 McLeskey are participating in this meeting as  
24 non-voting industry representatives, acting on  
25 behalf of regulated industry. Their role at this  
26 meeting is to represent industry in general and  
27 not any one particular company. Dr. Totman is an  
28 independent pharmaceutical consultant, and

1 Dr. McLeske is employed by Baxter Healthcare  
2 Corporation.

3 With regards to the FDA's guest speakers,  
4 the agency has determined that the information to  
5 be provided by these speakers is essential. The  
6 following interests are being made public to allow  
7 the audience to objectively evaluate any  
8 presentation and/or comments made by the speakers.

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

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

25 As guest speakers, Drs. Dargan and James  
26 will not participate in the committee  
27 deliberations, nor will they vote.

28 We would like to remind members and

1 temporary voting members of the committees that if  
2 the discussions involve any other products or  
3 firms not already on the agenda for which an FDA  
4 participant has a personal or imputed financial  
5 interest, the participants need to exclude  
6 themselves from such involvement, and their  
7 exclusion will be noted for the record.

8 FDA encourages other participants to  
9 advise the committees of any financial  
10 relationships that they may have with any firm at  
11 issue.

12 Thank you. And for the purpose of the  
13 transcriber, again today, if you are going to be  
14 speaking, if you can say your name into the  
15 microphone, please.

16 DR. NELSON: As most of you know, or at  
17 least was alluded to yesterday, the U.K. has had a  
18 specific interest in acetaminophen overdose and  
19 has made large public health gestures towards  
20 reducing the problem that they have there, and we  
21 actually have two guest speakers from the United  
22 Kingdom who are here to present -- or one of whom  
23 is here to present; the other is going to present  
24 by telecast -- the first speaker by telecast,  
25 Professor Keith Hawton, who is the director for  
26 suicide research at Warneford Hospital in Oxford.

27 DR. HAWTON: Shall I begin?

28 DR. NELSON: Yes.

1 DR. HAWTON: Thank you very much. First  
2 of all, I'd like to thank the committee for  
3 inviting me to give a presentation. I'm very  
4 sorry I couldn't be present to do it, but hope  
5 that, you know, doing this over a telecast will be  
6 satisfactory. Have I got my title slide up?

7 DR. NELSON: Your slide is up. Yes.

8 DR. HAWTON: Thank you. What I'd like to  
9 do in this presentation is to present background  
10 information that -- about what factors contributed  
11 to the 1998 U.K. legislation on paracetamol. I'll  
12 be referring to it as paracetamol rather than  
13 acetaminophen throughout.

14 I'll then say a few words about the  
15 rationale for the legislation, and then briefly  
16 summarize our findings regarding the evaluation of  
17 the impact of the legislation. I know Dr. Dargan  
18 will be dealing with the evaluative aspects more  
19 fully.

20 So if I could have the next slide,  
21 please.

22 In terms of the background, we had  
23 noticed in the U.K. a steady increase in  
24 paracetamol overdoses from the mid-1970s.

25 If I could have the next slide, please.

26 Can I just check that that shows  
27 substances used for non-fatal self-poisoning; is  
28 that correct?



1 DR. NELSON: That is correct.

2 DR. HAWTON: Thank you.

3 This slide shows data that we collected  
4 based on all presentations to the major general  
5 hospital in Oxford between 1976 and 1999. I  
6 established a monitoring system for collecting  
7 data on all cases presenting to the emergency  
8 department of the hospital, irrespective of  
9 whether they got admitted to a hospital bed or  
10 not -- I established this in 1976.

11 And you can see, from the graph, that the  
12 red line for paracetamol showed an increasing use  
13 of this drug -- this is including paracetamol  
14 compounds -- over the late 1970s, throughout the  
15 1980s, such that by the early 1990s nearly half of  
16 all overdoses were involving paracetamol.

17 Other centers in the U.K. reported  
18 similar statistics, although the level reached was  
19 more like 40 to 45 percent of all overdoses for  
20 paracetamol. We perhaps have a higher figure  
21 because we have a relatively large young  
22 population, and paracetamol overdoses tend to be  
23 more common in younger people.

24 Could I have the next slide, please.

25 The second point was that the increase in  
26 overdoses had clearly paralleled availability of  
27 paracetamol.

28 If I could have the next slide, please.

1                   This slide shows U.K. sales data for  
2                   paracetamol between 1983 and 1994 in green, on the  
3                   green line on the graph. This is plotted against  
4                   rates of paracetamol overdose, again, based on our  
5                   local data. And you can see that the years where  
6                   the data were available for both sales and  
7                   overdoses there was a very high correlation.

8                   Could I have the next slide, please.

9                   If you turn to the third point on this  
10                  slide, an important additional finding was that  
11                  the numbers of patients presenting to liver units  
12                  with paracetamol-induced hepatotoxicity had been  
13                  increasing steadily such that, by the mid-1990s,  
14                  there were between 30 and 40 liver transplants per  
15                  year in the U.K. for this specific indication.  
16                  And this became the most common reason for liver  
17                  transplantation in the U.K.

18                 And then the fourth point on the same  
19                 slide was that there were increasing numbers of  
20                 death such that, by the mid-1990s, there were  
21                 between 200 and 250 deaths per year involving  
22                 paracetamol and paracetamol compounds. And that's  
23                 excluding the prescription-only paracetamol/opiate  
24                 compound co-proxamol which includes  
25                 dextropropoxyphene, which I think is known as  
26                 Darvon or Darvocet in the U.S.A.

27                 Could I have the next slide, please.

28                 By the mid-1990s, serious consideration

1 was being given in this country to means of  
2 reducing the mortality and morbidity associated  
3 with paracetamol overdose. And I've listed on  
4 this slide some of the potential measures were  
5 considered. I'll just go through them very  
6 briefly. There was discussion of including an  
7 emetic agent in tablets. This was rejected  
8 because of possible negative effects at  
9 therapeutic levels.

10           There was considerable discussion about  
11 including the naturally-occurring amino acid  
12 methionine in tablets because of its protective  
13 effect against liver damage. This was eventually  
14 dropped because of potential dangers, including  
15 possible carcinogenicity based on rat models and  
16 concerns about effects on the fetus in pregnant  
17 women.

18           Blister packs -- the third points is  
19 about blister packs. Well, these were already  
20 being introduced throughout the 1990s. The fourth  
21 point is reduced pack sizing -- pack sizes which,  
22 of course, became the main component of our  
23 legislation -- and I'll discuss the reason for  
24 this shortly.

25           And then, finally, there was discussion  
26 about warnings on packs. Again, I will discuss  
27 this briefly later, but one point to raise here  
28 that was discussed at the time, and has been

1 discussed since, is the questionable evidence  
2 about how beneficial this is, particularly for  
3 people who may be feeling suicidal, that there is  
4 the potential for possibly increasing risk of an  
5 overdose. But this was introduced as part of the  
6 legislation.

7 Could I have the next slide, please?

8 I'd now like to turn to some of the  
9 research which influenced the MHRA in deciding  
10 upon our 1998 legislation, and I'm going to  
11 particularly refer to a study we did of 80  
12 patients who were interviewed. This is out of a  
13 potential sample of 105 patients, so we were able  
14 to recruit the vast majority of a consecutive  
15 series of patients who presented to hospital over  
16 paracetamol overdoses. This study was done during  
17 1992 and 1993.

18 And this first slide shows the  
19 characteristics of the sample. Two-thirds of them  
20 were female. This was predominantly a very young  
21 sample, 40 percent being age 13 to 20 and 40  
22 percent age 21 to 35. So 80 percent of the  
23 patients were under the age of -- were 35 or  
24 under.

25 Could I have the next slide, please.

26 Over 60 percent of patients, when asked  
27 the reason for choosing paracetamol -- and they  
28 were actually presented a list, so this was rather

1 than a spontaneous response -- they checked easy  
2 availability; over 60 percent checked easy  
3 availability as their main reason for choosing  
4 paracetamol rather than something else.

5 The overdoses often appeared to be  
6 impulsive in that 41 percent said they thought  
7 about taking the overdose for less than an hour  
8 beforehand. That doesn't mean they hadn't had  
9 suicidal ideas previously, but the specific  
10 thoughts about the overdose they said had only  
11 been present for less than an hour. And one-third  
12 said their thoughts about the overdose had been  
13 present for one to three hours.

14 Nearly two-third of patients knew that  
15 paracetamol could kill a person if taken in  
16 overdose, but as you will see from the slide, over  
17 half thought they would become unconscious -- and  
18 that was almost immediately unconscious as a  
19 result of taking the overdose, which clearly  
20 doesn't happen unless other drugs are consumed.

21 In the clinicians' opinions, 39 percent  
22 had suicidal intention rather than other motives  
23 for the act, such as taking an overdose in order  
24 to influence someone else or seeking -- taking an  
25 overdose to seek temporary oblivion, et cetera.

26 Could I have the next slide, please? Can  
27 I just check that I'm keeping -- the slides are  
28 matching what I'm saying.

1 DR. NELSON: They are so far. yes.

2 DR. HAWTON: Thank you.

3 The next slide shows the source of the  
4 tablets, and you can see that 40 percent, the  
5 tablets have been obtained from a pharmacy, not  
6 necessarily for the overdose. 24 percent have  
7 been obtained from other sales outlets. The rest  
8 had either been prescribed by a family doctor,  
9 which was true in ten cases. Or the source of the  
10 tablets wasn't known.

11 Approximately half the patients had  
12 actually bought the tablets for the purpose of the  
13 overdose. Others had used tablets that happened  
14 to be in the household.

15 If I could have the next slide, please.

16 This slide shows information relating to  
17 packaging of the overdoses. You can see nearly  
18 half the patients -- and I'll remind you, this is  
19 in the early 1990s when blister packing was  
20 starting to come in. Nearly half the patients  
21 used overdoses from loose preparations, but 60  
22 percent used tablets from blister packs. And the  
23 reason that the percentages add up to over 100  
24 percent was that some -- a few patients used a  
25 mixture of both tablets from loose and blister  
26 packs.

27 Secondly, the patients who took overdoses  
28 where the tablets were in loose containers tended

1 to take larger overdoses. And you can see that 69  
2 percent of those who took tablets from loose  
3 preparations consumed more than 25 tablets  
4 compared with 40 percent who used -- took tablets  
5 from blister packs.

6 And, thirdly, those who took larger  
7 overdoses tended to have higher suicidal intent.  
8 And here the score -- the scores shown are based  
9 on the scores on the Beck suicide intent scale, a  
10 regularly used measure for assessing suicidal  
11 intent in research and clinical practice.

12 Could I have the next slide, please.

13 Patients were asked about possible  
14 warnings on packs adduct whether they -- whether  
15 warnings would have influenced their decision to  
16 take an overdose. Now, clearly -- you know, this  
17 is based on the retrospective accounting of what  
18 the patients thought might have happened, not  
19 necessarily what would have happened.

20 And the warning showed in this slide,  
21 namely "an overdose of paracetamol can kill," was  
22 viewed as the most offputting of the ones that we  
23 presented them with. But, as you can see from the  
24 second bullet point, only a quarter of patients  
25 thought that any type of warning would have  
26 stopped them taking an overdose.

27 And then, with regard to the third bullet  
28 point, as I've already mentioned, while warnings

1 are almost certainly useful for regular users,  
2 there is the difficult problem of the possible  
3 potential dangers for depressed and suicidal  
4 people seeing such warnings and, therefore, the  
5 contents of any warning needs to be very carefully  
6 considered.

7 Could I have the next slide, please?

8 The findings of this study were quite  
9 influential in the MHRA decision to introduce  
10 legislation in 1998 which particularly focused on  
11 pack sizes. Now, I think you already have all the  
12 information about our legislation, but just to  
13 summarize -- well, the background factors that  
14 were particularly important were the impulsivity  
15 of many of the overdoses, or the apparent  
16 impulsivity involved, and the large amounts often  
17 available in households.

18 I should remind you that the legislation  
19 also involved aspirin and its compounds because  
20 there was concern about a possible switch for  
21 paracetamol to aspirin, which is probably more  
22 dangerous in overdose.

23 Now, as I say you know the details, but  
24 just to summarize, before the legislation,  
25 containers -- I'm sorry -- up to 100 tablets could  
26 be bought from pharmacies and 24 tablets from  
27 non-pharmacy outlets.

28 After the legislation, pack sizes were



1 restricted to a maximum of 32 from pharmacies and  
2 16 from non-pharmacy outlets. And with -- there  
3 were also labeling changes made to packs.

4 There was a voluntary code agreed by most  
5 of the sales outlets that they would restrict  
6 sales to one pack up to the maximum size imposed  
7 by the legislation. And, if I could turn to the  
8 next slide, this in a way summarizes the rationale  
9 behind the legislation. It shows the potential  
10 availability in schematic form of paracetamol or  
11 aspirin in households before the legislation, in  
12 red, when large amounts might have been bought,  
13 and then after the language in blue when more  
14 packets may have been purchased, but these would  
15 have been slower and, therefore, the number of  
16 tablets available at any one time in a household  
17 would, for most of the time, have been less than  
18 prior to the legislation.

19 And also purchases made for the purpose  
20 of overdose would have been generally smaller  
21 although, of course, people could go to multiple  
22 outlets if they wished.

23 And I think the sales data that we  
24 presented in our 2004 paper, in the BMJ, did  
25 actually reflect what is shown in that schematic  
26 sawtooth diagram.

27 Can I turn to the next slide, please?

28 This just summarizes what we found in our

1 evaluation which was published in 2004. I'll just  
2 go through it very briefly, as I know Dr. Dargan  
3 will address the evidence in more detail. This  
4 was based -- this study was based on data on all  
5 self-poisoning presentations, including patients  
6 who were managed in the emergency department and  
7 not actually admitted -- for all self-poisoning  
8 presentations to seven large general hospitals.  
9 Secondly, data from liver units in the United  
10 Kingdom. And, thirdly, mortality data from  
11 England and Wales -- and I should emphasize that  
12 co-proxamol, the preparation containing  
13 paracetamol and the opiate dextropropoxyphene was  
14 omitted from this.

15 And just to summarize those findings, we  
16 found that the numbers of tablets taken in  
17 overdoses, and also large overdoses, of both  
18 paracetamol and aspirin significantly decreased,  
19 that admissions to liver units and also liver  
20 transplants decreased by about 30 percent, and  
21 that deaths from paracetamol and salicylate  
22 self-poisoning -- aspirin self-poisoning, sorry,  
23 in England and Wales decreased by 22 percent over  
24 the three-year period following the legislation,  
25 which we estimated equated to 199 fewer deaths.

26 We did try to look at substitution by  
27 other methods -- this is rather difficult in the  
28 sense that there are quite a large number of

1 methods that one could look at. The numbers --  
2 the reduced number of deaths is, of course, still  
3 relatively small.

4 We did find an increase in purchases and  
5 deaths involving the NSAID ibuprofen, but when we  
6 looked at those closely, the numbers involved were  
7 relatively small and, in every case, another drug  
8 or substance had been taken which was more likely  
9 to have been the lethal agent. So we didn't think  
10 that the increase in NSAID overdoses had  
11 contributed to a compensatory mortality following  
12 the legislation.

13 And if I could have my final slide.

14 This shows the deaths per year for  
15 paracetamol alone -- well, it could include  
16 alcohol, but not other drugs -- for England and  
17 Wales for two periods prior to the legislation --  
18 so 1993 to 1996, 1996 to 1998 where you could see  
19 the numbers of deaths had increased. So this  
20 doesn't include compounds, which would have  
21 contributed quite a substantial number of further  
22 deaths.

23 Then you can see the apparent impact of  
24 the legislation in the 1998 to 1999 period, and  
25 then the number of deaths thereafter remained at  
26 approximately the same level. I think the 2007  
27 data are incomplete, and we should perhaps ignore  
28 the 2007 data.

1                   So I show you this because not only does  
2                   it appear to show a downturn in deaths following  
3                   the legislation, but it also shows that there are  
4                   still quite a large number of deaths -- 120 to 130  
5                   per year -- from pure paracetamol overdose, and  
6                   probably another 50 to 60 from overdoses involving  
7                   compounds.

8                   And one question that we're looking at at  
9                   the moment is whether the maximum size of packs is  
10                  set too high, particularly the 32-tablet limit  
11                  from pharmacies, and whether a lower limit might  
12                  have had a more substantial effect.

13                  In Ireland, as you probably know, a limit  
14                  of 24 tablets was introduced, and there are  
15                  reasons for believing that possibly a lower limit  
16                  might have been more effective as pharmacokinetic  
17                  have shown that the risk of hepatotoxicity  
18                  increases very substantially once someone takes  
19                  more than about 28 tablets.

20                  But that's a question, you know, we're  
21                  looking into at the moment, and I don't have any  
22                  answers to whether that would be a good thing or  
23                  not.

24                  So with that, I end my presentation. I'd  
25                  be very happy to take any questions.

26                  DR. NELSON: Well, thank you very much.  
27                  I do have a question, and the question is if  
28                  you'll be able to hang on the line for about 15

1 minutes to take questions with the group, or do  
2 you feel you need to leave and we'll ask you  
3 questions now?

4 DR. HAWTON: No, I'd be happy to take  
5 them -- is Dr. Dargan going to present next?

6 DR. NELSON: That's right. And this way  
7 we can get, you know, all of the questions  
8 directed to both of you --

9 DR. HAWTON: I'd be very happy with that.

10 DR. NELSON: Okay. That would be  
11 wonderful. Thank you.

12 The next speaker, then, is Dr. Paul  
13 Dargan, who is the clinical director for  
14 toxicology at Guy's and St. Thomas' NHS Foundation  
15 Trust in London.

16 DR. DARGAN: Thank you, Lewis, and thank  
17 you to the FDA and to the committee for inviting  
18 me to speak to you today.

19 I'm going to carry on from where  
20 Professor Hawton has left in setting the scene  
21 behind the legislation and looking at the studies  
22 that have been published in the U.K. on the impact  
23 of the legislation on paracetamol acetaminophen  
24 poisoning. Like Professor Hawton, I'm going to  
25 apologize in advance for using the term  
26 "paracetamol" throughout. It's sort of force of  
27 habit, and to slip between acetaminophen and  
28 paracetamol I'm afraid is something I would find

1 difficult, so I'm going to stick to paracetamol  
2 throughout.

3 Professor Hawton has already described  
4 the legislation in some detail, so I won't go  
5 through this slide other than to say that there  
6 was no systematic process put in place to monitor  
7 the impact of the legislation. So the studies  
8 were all designed in different ways on an ad-hoc  
9 basis rather than planned studies prior to the  
10 legislation that were able to look systematically  
11 at the impact of the legislation.

12 There have been numerous studies  
13 published since 1998 to try and look at the  
14 impact. And I guess they've looked at them in two  
15 different ways. Firstly, the number of  
16 paracetamol poisonings, the number of hospital  
17 admission, the number of calls to poison centers,  
18 and then the size of the overdose, the number of  
19 tablets taken, the plasma paracetamol  
20 concentration, the number of patients needing  
21 treatment with N-acetylcysteine, the number  
22 developing hepatotoxicity and requiring transfer  
23 to or management in a liver unit or liver  
24 treatment, and ultimately the number of deaths  
25 related to paracetamol poisoning.

26 Before I talk about the studies, I wanted  
27 to talk about some of the sort of limitations to  
28 sort of set the scene, I suppose.

1           Most of the national systems looking at  
2           hospital admissions only capture hospital  
3           admissions. They don't capture emergency  
4           department presentations. Unlike Professor  
5           Hawton's studies, which were much more detailed  
6           and looked at -- included emergency department  
7           presentations, the national systems in the U.K.  
8           don't. Therefore, patients that are managed  
9           purely in the emergency department won't be  
10          captured. Those with smaller overdoses and those  
11          who don't require treatment with N-acetylcysteine  
12          and are discharged rapidly won't be captured by  
13          the national systems.

14                 And there have been significant changes  
15                 in the way that patients are managed within the  
16                 emergency department in the last ten years or so,  
17                 which influences the way that these data systems  
18                 will capture patients.

19                 There was another set of legislation in  
20                 the U.K. in the early 2000s mandating that all  
21                 patients had to be -- a decision had to be made on  
22                 their movement from the emergency department  
23                 within four hours. Therefore a patient would  
24                 be -- if they were going to be admitted, they  
25                 would be admitted at four hours -- before four  
26                 hours post presentation to the emergency  
27                 department. So that will color the data that's  
28                 available on hospital admissions.

1           There's relatively poor coding in most of  
2           the data sets of deliberate self-poisoning versus  
3           unintentional poisonings so almost all of these  
4           studies are looking at total paracetamol  
5           poisoning.

6           And in the U.K. 90 to 95 percent of  
7           paracetamol poisoning is deliberate  
8           self-poisoning. 5 -- maybe 10 percent, at the  
9           very most, is unintentional poisoning. So most of  
10          what we are looking at here is deliberate  
11          self-poisoning or total paracetamol poisoning.

12          There were clearly some limitations in  
13          the mortality data sets that hold throughout the  
14          worlds, and those are probably known to most  
15          people in this audience, and there's a substantial  
16          literature on the limitations in mortality --  
17          drug-related mortality data sets in terms of  
18          ascribing single drugs to a cause of death.

19          And most of the data sets don't separate  
20          over-the-counter lone paracetamol preparations  
21          that are covered by the legislation from mixed  
22          paracetamol ingestions -- the paracetamol/opioid  
23          combinations which are prescription-only  
24          combinations.

25          And also, even though paracetamol is  
26          widely available over-the-counter, many patients  
27          will still be getting on prescription from their  
28          primary care practitioner, and so some of the



1        paracetamol that is available in the community is  
2        available -- even though it's lone paracetamol --  
3        is available as prescription paracetamol in  
4        addition to over-the-counter paracetamol.

5                In terms of the studies themselves, many  
6        of them have relatively short-term follow-up after  
7        the legislation -- and I'll come back to that a  
8        little bit later. And as I said, there was no  
9        sort of systematic process put in place to have a  
10       system looking at the impact of the legislation,  
11       so there are many different study designs,  
12       different data sources, different outcomes  
13       measurements, and so pooling the data from the  
14       studies is relatively difficult because of that.

15               The minority of the studies used a  
16       control to look at paracetamol poisoning  
17       relative -- changes relative to deliberate  
18       self-poisoning as a whole and whether changes in  
19       paracetamol poisoning may have been associated  
20       with changes in poisoning with other agents  
21       available over-the-counter or available on  
22       prescription.

23               And no studies in the U.K. have looked at  
24       the potential switch effect from therapeutic  
25       paracetamol to therapeutic NSAIDs with their  
26       potential gastrointestinal or renal or cardiac  
27       effects in therapeutic use. All of the data  
28       really has looked at overdose rather than

1 therapeutic changes.

2           The first study I'm going to present is a  
3 study from my unit where we looked at calls to our  
4 poison information center. We focused purely on  
5 the number of tablets ingested or number of  
6 reported tablets ingested in lone paracetamol  
7 overdose, so these we excluded the  
8 paracetamol/opioid combinations. We were just  
9 looking at lone paracetamol overdoses. Clearly,  
10 some of these patients had taken other agents in  
11 overdose as well, but the paracetamol they had  
12 taken was lone paracetamol.

13           As I mentioned before, insufficient  
14 coding to be able to differentiate between  
15 intentional and unintentional. So this is all  
16 paracetamol poisoning, although the majority of it  
17 is intentional deliberate self-poisoning.

18           Unfortunately, there were changes in U.K.  
19 poisons information delivery during this time  
20 period, so it's not really a population study. At  
21 the beginning of the study, we were a national  
22 unit taking calls from throughout the country.  
23 Towards the end of the study we were more of a  
24 regional unit, taking calls from around our  
25 center. So we can't really look on a population  
26 basis at the impact of the legislation, but we --  
27 you know, there clearly is, from the size of the  
28 number of calls, that we have the ability to be

1       able to look at impact overall.

2               And also, clearly, clinicians don't call  
3       a poison center about all cases. They tend to  
4       call about the more severe end of the spectrum, or  
5       for other reasons, and so there are limitation in  
6       poison center databases.

7               We had 140,000 calls relating to  
8       paracetamol poisoning. These are all from  
9       clinicians. We don't have public access to poison  
10      centers in the U.K., so these are all patients in  
11      emergency departments having taken excessive  
12      paracetamol. 140,000 calls. Data on dose  
13      ingested available in just over 100,000 of these,  
14      about 80 percent of the patients. There was a  
15      2-gram decrease in the number of -- in the dose of  
16      paracetamol ingested from 1999 onwards, and that  
17      was a reasonably sustained in the dose of  
18      paracetamol ingested in both males and females.

19              From a clinical perspective, that's a  
20      modest decrease, but clearly that will be a  
21      population who were on the threshold of a toxic  
22      dose, where a 2-gram decrease will make a  
23      difference. But overall, from a clinical  
24      perspective, 2 grams is a modest decrease.

25              If we then look at the number of  
26      individuals who have taken very small versus --  
27      very small and non-toxic versus much higher and  
28      potentially clinically significant hepatotoxic

1 overdoses, there was a significant increase in the  
2 numbers who had taken very small overdoses, so  
3 less than 16 tablets, potentially one pack, of  
4 non-pharmacy outlet paracetamol, from 38 percent  
5 to 50 percent.

6 And there were decreases in the numbers  
7 that had taken moderate ingestion, so two packs --  
8 up to two packs of paracetamol -- and taken the  
9 clinically significant ingestion. So from 36 to  
10 30 percent of the moderate ingestions, and 25 to  
11 19 percent of the much larger ingestions. So, you  
12 know, clearly there are going to be significant  
13 numbers of individuals within these groups of  
14 which the decrease in dose is going to be  
15 clinically significant. But there are still  
16 significant numbers of individuals who have taken  
17 very large, potentially hepatotoxic doses.

18 The next thing I'm going to go on to  
19 present is a literature review that we published a  
20 couple of years ago, now, in drug safety. And  
21 this identified 17 studies in the U.K. that had  
22 looked at the impact of the paracetamol pack size  
23 legislation. There have only been two studies  
24 published since, and I'm going to briefly mention  
25 those as well.

26 I already mentioned the follow-up issue.  
27 11 of the 17 studies had relatively short  
28 follow-up. Only the first two years after the

1       legislation. Mean follow-up of just under  
2       two-and-a-half years. Different study designs,  
3       different data sources and different outcome  
4       measures -- looking at some of the issues that  
5       I've already highlighted in terms of size of the  
6       overdose and numbers of patients.

7               So if we look first at mortality --  
8       Professor Hawton presented some of the data from  
9       his group and from his -- one of the larger  
10       studies, the BMJ study that he published in 2004.  
11       There have been eight studies that have been --  
12       that were in our review, and there have been two  
13       more recent studies that I'll mention briefly in a  
14       moment.

15               Three of them showed some reduction in  
16       mortality -- these were studies in England and  
17       Wales -- three no difference in mortality -- one  
18       of these in England, two of them in Scotland. One  
19       showed an initial reduction, followed by an  
20       eventual increase, so in the first two years after  
21       legislation there was a decrease in mortality, and  
22       then an increase back to the baseline -- back to  
23       the baseline mortality.

24               One, the most recent study, showed an  
25       overall increase in mortality -- this was in  
26       Scotland. And I'll come back to the England/Wales  
27       versus Scotland issue as we come through the  
28       presentation.

1                   There has been a more recent study  
2 published by Oliver Morgan a couple of years ago  
3 that looked at paracetamol poisoning mortality  
4 related to other poisoning mortality and to  
5 non-poisoning mortality.

6                   The lone paracetamol poisoning mortality  
7 is the black boxes here. Non-poisoning suicide  
8 mortality is the clear circles at the top of the  
9 slide. And they also looked at antidepressant  
10 mortality, paracetamol compound mortality,  
11 paracetamol/opioid combinations, removing, again,  
12 co-proxamol because of the issue with  
13 dextropropoxyphene poisoning -- and looked at  
14 aspirin poisoning as well.

15                  And you can see from this graph that all  
16 of these lines basically follow the same  
17 trajectory. And they did statistics looking at  
18 these trajectories, and they do indeed follow the  
19 same trajectory.

20                  Unfortunately, some of the controls are  
21 potentially also biased as well.  
22 Antidepressants -- there has been a change  
23 internationally from tricyclics to SSRIs which  
24 have relatively lower mortality which may compound  
25 that.

26                  If you look at non-drug suicide, carbon  
27 monoxide with a change to catalytic converters,  
28 there's a potential that you're decreasing carbon

1       monoxide poisoning. So there's some bias in some  
2       of the control groups, but it's interesting that  
3       the paracetamol poisoning mortality follows the  
4       same sorts of decreases as all of the other drug  
5       mortalities, suggesting that this may be part of a  
6       wider trend in changes in suicidal behavior rather  
7       than directly related to the legislation.

8               Another more recent study looked at  
9       hospital admissions and deaths in Scotland. This  
10      is a large study, looking across the population in  
11      Scotland of both admissions -- and these are all  
12      admissions, including emergency department  
13      presentations and deaths.

14             If you look at the graph here, the  
15      legislation was towards the end of 1998, and  
16      potentially there was a small decrease. These are  
17      total hospital admissions and deaths, so this is  
18      looking at the combined data set.

19             There was a small decrease in the first  
20      year or so in all of the quintiles, from the more  
21      deprived quintiles at the top of the graph here,  
22      to the less deprived quintiles at the bottom of  
23      the graph, in the first year or so after the  
24      legislation. But this increased back to baseline  
25      in the next year or two. And by four years post  
26      legislation in all of the quintiles was back to  
27      the baseline death rate and hospital admission  
28      rate.

1                   And when you look at the proportion of  
2                   paracetamol poisoning relative to all poisoning,  
3                   this increased after the legislation. So 30  
4                   percent of all overdoses presenting to hospital  
5                   were paracetamol-related in Scotland in 1997, 35  
6                   percent in 2002, suggesting that the impact of the  
7                   legislation across Scotland as a whole is really  
8                   very limited and was greatest in the first year or  
9                   two after the legislation.

10                  Of interest, the majority of the deaths  
11                  and hospital admission are in the more deprived  
12                  quintiles.

13                  So we've looked at mortality. Let's now  
14                  look at hepatotoxicity. Seven studies looked at  
15                  liver unit admission and/or transplantation. Five  
16                  showed some degree of reduction. Two showed no  
17                  change. One of the no-change studies was in  
18                  Scotland.

19                  Professor Hawton has already presented  
20                  his data looking at liver transplants and liver  
21                  unit admissions, so I won't present this again.  
22                  The Prince -- in Professor Hawton's study, he  
23                  looked at six of the seven liver units. The  
24                  Prince study is the only national study that  
25                  looked at all of the liver units. They showed a  
26                  decrease in the number of liver unit referrals,  
27                  from three-and-a-half to two per month.

28                  But this decrease started in 1997, before



1 the legislation. There was already starting to be  
2 a decrease. The magnitude of that decrease  
3 decreased after the legislation, but the decrease  
4 was already there prior to the legislation, again,  
5 suggesting that there's something else going on,  
6 as opposed to just purely it being  
7 legislation-related.

8 What about hospital admission studies?  
9 Seven studies, three reporting some degree of  
10 reduction in hospital admissions of the order of 5  
11 to 10 percent in all of these -- 5 to 15 percent  
12 in all of these studies.

13 One Scottish study, an initial decline  
14 and then a subsequent increase, one Scottish study  
15 reporting an increase in admissions, one England  
16 and Wales study reporting a decrease in  
17 paracetamol admissions, but a corresponding  
18 increase in ibuprofen poisoning admissions, one  
19 England and Wales study reporting a decrease in  
20 paracetamol admissions but an increase in overall  
21 non-paracetamol poisoning admissions.

22 Clearly some of -- the interpretation of  
23 some of these is colored from the limitation that  
24 I've discussed at the beginning, but again,  
25 suggesting that there was a mixed impact of the  
26 legislation and, you know, it was a small impact  
27 rather than an enormous impact in terms of overall  
28 hospital admissions.

1                   So, in summary, in terms of the impact of  
2                   the legislation, modest reduction in mortality,  
3                   still of the order of 80 to 110 deaths per year  
4                   from paracetamol poisoning. May potentially be  
5                   part of a wider trend in suicide and poisoning  
6                   deaths.

7                   Hepatotoxicity, a modest, non-sustained  
8                   reduction -- still 20 to 25 transplants per year.  
9                   And potentially this decrease started before or --  
10                  you know, there may have been other factors  
11                  impacting on the hepatotoxicity decrease.

12                  Dose ingested. Modest decrease, 1 to 2  
13                  grams, potentially of minimal clinical  
14                  significance when you look at the population as a  
15                  whole, but clearly of an impact to those on the  
16                  cusp of toxicity.

17                  Admissions. Small, non-sustained  
18                  decrease in admissions in England and Wales, but  
19                  not in Scotland. Remains common, still 20,000  
20                  admissions per year in the U.K. Still of the  
21                  order of 35 to 40 percent of all poisoning is  
22                  paracetamol-related.

23                  And there's the suggestion that there may  
24                  have been an increase in non-paracetamol  
25                  poisoning, although that data is relatively flimsy  
26                  and only from one or two of the studies.

27                  I won't talk about the paracetamol sales  
28                  data, because I know that's within your packs and

1 Professor Hawton briefly mentioned it before, but  
2 I just wanted to briefly mention -- has the  
3 legislation actually reduced the amount of  
4 paracetamol that's available in the home and also  
5 that's available to buy for impulsive deliberate  
6 self-poisoning ingestions? Because I think this  
7 is important.

8 We did a study where a group of medical  
9 students went around some shops in our local area  
10 and attempted to buy 64 paracetamol tablets. How  
11 easy can people just go into a shop and say, I  
12 want 64 tablets? The legislation -- as Professor  
13 Hawton said, there was a voluntary code that  
14 non-pharmacy outlets should be selling only one  
15 pack of 16, and pharmacy outlets should only be  
16 selling one pack of 32 or two packs of 16. So  
17 this is against the voluntary code, but isn't  
18 actually against the legislation per se. The  
19 legislation only mandated pack sizes themselves.

20 In half of the pharmacies we were able to  
21 buy more than 32 tablets, 48 in three and 64 in  
22 one. In the majority of supermarkets, petrol  
23 stations, news agents, non-pharmacy outlets we  
24 were able to buy more than 16 tablets. And, you  
25 know, significant numbers more than 16 in most of  
26 the outlets.

27 Overall, 70 percent of the outlets sold  
28 us more than 32 paracetamol. Half of them sold us

1 more than 48. And a fifth of them were selling us  
2 64 tablets. And that's been replicated in other  
3 studies since, including studies in Northern  
4 Ireland and studies in Scotland.

5 What about patients presenting with  
6 poisoning -- where do they get their paracetamol  
7 from? Well, we asked 109 of our patients with  
8 paracetamol poisoning where they got their  
9 paracetamol from. This is a study we did in 2003,  
10 so five years after the legislation that was  
11 published in 2005 [sic].

12 Half of them had paracetamol stored at  
13 home. Clearly the pack size limitations may have  
14 some impact there, but, you know, a lot of people  
15 have multiple packs of paracetamol in different  
16 areas of the home or in their briefcase or in  
17 their office or in, you know, in other areas. And  
18 about half of them had purchased the tablets  
19 specifically for overdose. 11 percent of them had  
20 purchased 32 tablets from a pharmacy. 43 percent  
21 of them -- almost half of them -- had purchased  
22 paracetamol from different stores. So they had  
23 gone into one store, and they had only been able  
24 to get one or two packets, and then they had gone  
25 into another store a few hundred yards down the  
26 road or, you know, across the street, and they'd  
27 been able to buy another pack.

28 I think that's one of the main problems,

1 particularly in terms of intentional poisoning,  
2 and if you want to get paracetamol, it's widely  
3 available -- okay, in smaller packs, but in  
4 multiple outlets and, therefore, clearly the  
5 overall impact is potentially colored for that  
6 reason. And about half of patients had been able  
7 to get more than 32 tablets in one store.

8 So clearly it's still -- even though the  
9 pack size limitations are there, it's still  
10 possible to buy relatively large amounts of  
11 paracetamol if you want -- if you want to do so,  
12 either from single outlets or from multiple  
13 stores.

14 I'm conscious of time, Lewis, and I've  
15 got a little bit of data on paracetamol.

16 I wanted to finish with a couple of  
17 slides looking at some of the published data on  
18 patient knowledge of paracetamol use and  
19 paracetamol content of available analgesics. And  
20 there's some U.S. data and some U.K. data, the  
21 first of them published last year, looking at a  
22 survey of just over 1,000 emergency department  
23 patients. Over half -- and this was looking at  
24 their knowledge of the acetaminophen content of --  
25 I think it was 14 or 15 different over-the-counter  
26 acetaminophen-containing products.

27 Just over half of them didn't know that  
28 Tylenol contains acetaminophen, and over half of

1       them didn't know the maximum daily dose of  
2       acetaminophen. So clearly if individuals are  
3       using products that they don't know contain --  
4       particularly if they're using multiple products,  
5       and they're not aware that they contain  
6       acetaminophen, and also they're not aware of the  
7       maximum daily doses, the potential for significant  
8       issues in terms of unintentional acetaminophen  
9       poisoning.

10               Replicated in a smaller study of patients  
11       attending an internal medicine clinic, about 40  
12       percent of whom didn't know that Tylenol contains  
13       acetaminophen, and only 2 percent of them were  
14       able to state the correct daily dose of  
15       acetaminophen. And in both of these studies there  
16       were a significant proportion of individuals who  
17       were saying that the maximum daily dose of  
18       acetaminophen was 8 or 10 grams, so up into the  
19       potentially toxic range.

20               Another two studies published in the last  
21       two or three years, looking at patients within the  
22       emergency department, and patients within dental  
23       clinics -- and many of the individuals that we see  
24       with unintentional paracetamol poisoning in the  
25       U.K. are those with dental pain who are taking  
26       multiple compounds. 5 to 10 percent of them  
27       reported that they had taken supertherapeutic  
28       doses of acetaminophen and other analgesics so

1 clearly it's a significant issue out there.

2           Similar it is in the U.K. A survey that  
3 we've done of 400 -- and we've actually increased  
4 this now in recent weeks to greater numbers --  
5 half the patients are aware of the correct maximum  
6 daily dose of paracetamol. Almost a third of  
7 patients think that ibuprofen contains  
8 paracetamol. Tylenol is a common compound in the  
9 U.K., I suppose similar to Tylenol in terms of its  
10 availability. 15 percent are aware that Tylenol  
11 contains paracetamol. 68 percent aware that  
12 Lemsip, which is a cough/cold medication that's  
13 very, very commonly used in the U.K. contains  
14 paracetamol. So there's a significant knowledge  
15 gap out there in terms of the maximum daily dose  
16 of paracetamol and the paracetamol content of  
17 analgesics and cough/cold remedies.

18           So, in conclusion, paracetamol poisoning  
19 remains common in the U.K. The pack size  
20 legislation has had an impact, but the impact has  
21 been relatively limited, particularly so in  
22 Scotland. It's still possible to buy multiple  
23 packs of paracetamol, either in single or in  
24 multiple outlets, and I think one of the issues is  
25 also that public knowledge of paracetamol use  
26 appears to be relatively poor on both sides of the  
27 Atlantic. Thank you.

28           DR. NELSON: And thank you -- thank you

1 both, actually.

2 I'd like to spend about ten minutes,  
3 perhaps, asking some questions of [sic] the  
4 committee. Just one quick question. What size is  
5 the paracetamol tablets that you sell? Are they  
6 each 325 milligrams or 500?

7 DR. DARGAN: 500.

8 DR. NELSON: Okay. Questions?

9 Dr. Wolfe.

10 DR. WOLFE: Sidney Wolfe here. Amongst  
11 the things being considered by the FDA and by this  
12 committee are, A, reducing size of the individual  
13 pill from 500 to 325 and, B, for the same reason,  
14 the dose from 1,000 to 625.

15 The other thing that's being considered  
16 is the uncoupling or banning of combination  
17 over-the-counter acetaminophen -- paracetamol --  
18 products.

19 I'd just like your comment on that, and  
20 coupled with that would be the idea that there  
21 seems to be a different proportion of people in  
22 the U.K. who are intentionally using  
23 acetaminophen -- paracetamol -- than here. It  
24 seems to be 90-plus percent whereas, here, it  
25 seems to be lower. But just -- the first part of  
26 the question is what about the lowering of the  
27 size of the tablet and the dose and the  
28 disallowing over-the-counter combination products?



1 DR. DARGAN: Keith, I don't know whether  
2 you want to --

3 DR. HAWTON: I'd rather comment on the  
4 second part of this, if that's okay.

5 DR. DARGAN: I think, from a  
6 toxicological -- clearly, there are two issues  
7 here, if you're looking at a dose decrease. From  
8 a toxicological perspective, in terms of looking  
9 at the population that take this in overdose,  
10 whether it be deliberate poisoning or  
11 unintentional poisoning, that potentially has a  
12 benefit.

13 But I must admit that I am less aware of  
14 the data that is available -- I know that it was  
15 in the pack and that it was discussed yesterday on  
16 the therapeutic efficacy of lower doses of  
17 acetaminophen. And I guess we're looking at a  
18 minority of individuals who take it in overdose,  
19 whether it be deliberate or unintentional, versus  
20 a huge population that are taking acetaminophen  
21 safely in therapeutic use, and we want them to be  
22 getting maximum therapeutic benefit.

23 I can't comment on that group, but I can  
24 comment on the deliberate poisoning and  
25 unintentional poisoning group where, potentially,  
26 a decreased dose, whether that be from pack size  
27 limitation, availability or decreased dose unit  
28 size, may have some impact. But I think that it

1 would have the same caveats as we've seen from the  
2 pack size limitations in the U.K. that the limits  
3 would be moderate rather than -- or are likely to  
4 be moderate rather than enormous.

5 In terms of the unintentional versus  
6 deliberate, there are a number of data sets in the  
7 U.K. that suggested it's of the order of 5 to 10  
8 percent, and those are similar to data sets from  
9 Australasia and other areas of Europe, and so it's  
10 difficult to understand why there is a significant  
11 different in the proportion of unintentional  
12 versus deliberate in Europe, Australasia versus --  
13 versus the U.S.; whether that may in some way be a  
14 coding issue as opposed to an absolute difference  
15 is difficult to comment on because I'm not aware  
16 of where that data comes from in the U.S. And  
17 Keith was going to comment --

18 DR. HAWTON: Can I comment on that last  
19 point? I mean, I think -- we've been very  
20 intrigued by the proportion of cases in the  
21 U.S. -- in the United States where acetaminophen  
22 overdose has been said to be accidental. And I  
23 must confess we've been quite questioning of how  
24 accurate those data are, particularly as I think  
25 there's been a change in the proportions reported.

26 I know Dr. William Lee's work has seemed  
27 to have shown an increase in the proportion now  
28 being regarded as intentional, although still a

1 large proportion being regarded as accidental.

2 And I think one would like to know much  
3 more about those cases, and maybe some direct  
4 study of people presenting with acetaminophen  
5 overdose of the kind that we've done where we  
6 interrogate people fairly carefully about their  
7 intentions and so on would be warranted.

8 I don't want to suggest that, you know,  
9 the data are inaccurate, but it is possible, as  
10 Dr. Dargan said, that they could be inaccurate.  
11 They are so discrepant with those -- you know, the  
12 data from -- as he said, from the U.K. and other  
13 countries.

14 DR. NELSON: Thank you. Dr. Gellad.

15 DR. GELLAD: Thanks. Walid Gellad. I  
16 was wondering, in the spirit -- for both of the  
17 speakers -- of not just what happened to those  
18 patients who overdosed, but what was the effect --  
19 do you know what the effect was of reducing  
20 package size on those who take it for therapeutic  
21 reasons? And one specific question might be, for  
22 example, about costs. Were there changes in the  
23 cost per tablet when you decreased the package  
24 size? Or any other effects it might have on those  
25 who take it therapeutically.

26 DR. DARGAN: There's no published  
27 literature that's really looked at therapeutic use  
28 of over-the-counter analgesics or -- that I'm

1       aware of -- that's looked at the impact of the  
2       legislation on therapeutic use of over-the-counter  
3       analgesics. I don't know whether Keith can add  
4       anything.

5               DR. HAWTON: No, I don't know of any,  
6       but -- I mean, paracetamol is still very cheap to  
7       buy, but I suspect in price per unit tablet, that  
8       the price has gone up considerably, if you see  
9       what I mean. That, you know, to buy a single  
10      container is quite cheap, but compared with buying  
11      loose containers of 100 tablets in the old days, I  
12      guess the unit cost has gone up quite  
13      considerably, but I don't think in a prohibitive  
14      sense for the average purchaser.

15             DR. DARGAN: I suppose along those lines,  
16      the one area that, in a way, indirectly answers  
17      that issue is the number of tablets sold. I mean,  
18      the three studies are conflicting in terms of the  
19      overall sales data, but there were 500-or-so  
20      tablets per year pre-legislation, and there are  
21      400 to 500 million tablets per year  
22      post-legislation. So the numbers are relatively  
23      similar. They may be slightly lower, but they are  
24      relatively similar in terms of overall numbers  
25      sold, so suggesting it hasn't had an enormous  
26      impact on decreasing therapeutic use or  
27      therapeutic availability.

28             DR. NELSON: Dr. Krenzelok.

1 DR. KRENZELOK: Krenzelok. Thank you  
2 very much.

3 In our briefing materials there's a paper  
4 that what is the embargo section of the materials  
5 by Professor Nick Bateman from Scotland, and it's  
6 entitled Limiting Paracetamol Pack Size: Has It  
7 Worked in the U.K.?

8 I called Dr. Bateman last week and asked  
9 him if it would be okay to share the information  
10 from this embargoed paper, which will be published  
11 probably this week in Clinical Toxicology, and  
12 Dr. Bateman concluded that paracetamol pack size  
13 limitation, as applied in the U.K., has not  
14 reduced paracetamol-related deaths. Reasons  
15 postulated for this failure include patient  
16 avoidance of the legislation's intention, patient  
17 confusion and ineffectiveness of the regulations  
18 as conceived and implemented.

19 And I'm wondering if Professor Hawton and  
20 Dr. Dargan could comment on this and basically --

21 DR. HAWTON: Can I come in?

22 DR. KRENZELOK: In just one second,  
23 please.

24 I'm wondering if you feel that such a  
25 major mitigation effort has really been  
26 justifiable.

27 DR. DARGAN: Keith, do you want to start?

28 DR. HAWTON: Yes. Sure. I missed a

1 little bit of that towards the end, but I think I  
2 got the gist. I mean, I don't know quite how  
3 Dr. Bateman reaches that decision, but one -- I  
4 mean, I'd really like, I guess, to comment in a  
5 way on one or two of the points made by Dr. Dargan  
6 which reflect on that.

7 I mean, the first thing is that we've  
8 talked about the 1998 legislation -- and being  
9 very precise, you know, it was September 1998 --  
10 as if there was a sort of -- a change at that  
11 point.

12 I mean, actually what happened was that  
13 there was already recognition that things were  
14 going to change. And some of the changes that  
15 eventually were in the legislation were already  
16 happening in terms of reduced pack sizes and so  
17 on.

18 So I think one has to be wary about  
19 interpreting data which don't appear to show an  
20 abrupt change towards the end of 1998. And I  
21 noticed Dr. Dargan's comment about, you know, the  
22 liver unit findings, that these started to -- they  
23 noticed that these were happening in 1997. And  
24 that doesn't surprise me at all.

25 The second thing is that some --  
26 something has been made of the fact that the  
27 number of overdoses of paracetamol has not  
28 decreased markedly, although it did show a bit of

1 a downturn around the time of the legislation.  
2 This is not surprising. This wasn't the aim of  
3 the legislation. It was about, in a sense, trying  
4 to make paracetamol overdoses more safe, if you  
5 like, by trying to ensure that the number of  
6 tablets taken was fewer.

7 And I think -- and Dr. Dargan has  
8 commented on this -- that while the change in the  
9 average size of overdoses was relatively modest,  
10 as he has commented, at a population level are  
11 actually going to have a very significant effect  
12 and I think will be compatible with the sort of  
13 results we got.

14 And, in particular, the number of large  
15 overdoses was considerably reduced. So it wasn't  
16 just a shift to the left, but a particular shift  
17 at the upper end, which would be expected to have  
18 quite an effect on hepatotoxicity and death.

19 Another point is that comparison is often  
20 made between England and Wales on one hand and  
21 Scotland and -- Scotland particularly, and also  
22 Northern Ireland. I'd like to remind you that  
23 Scotland is -- only has a population some  
24 one-twelfth that of -- or maybe a bit more than  
25 that -- but of England, and Northern Ireland is  
26 much smaller. And that it could be argued that  
27 the -- you know, the effect is only detectable  
28 where you have a very large sample examined,

1       namely a national sample of the sort of size we  
2       have in England and Wales.

3               And I noticed, looking through the -- you  
4       know, looking through the studies, that those that  
5       seem to have shown a positive effect has generally  
6       been based on national data -- that's not entirely  
7       true -- national data, either for liver units  
8       and/or for mortality. And I do want -- I think  
9       it's important to emphasize those points.

10              As I say, I haven't seen Bateman's paper,  
11       so I can't comment on how he's justified that  
12       conclusion, but I must say it is at variance with  
13       the way that we and colleagues have viewed the  
14       current information.

15              DR. DARGAN: I, too, haven't seen the  
16       paper that's currently in press and not yet  
17       published in Clinical Toxicology, although I think  
18       that -- when you look at the studies as a whole,  
19       either the 17 studies in our literature review and  
20       the two studies that have been published since, I  
21       would veer towards the conclusions of Professor  
22       Bateman that the impact has been relatively  
23       minimal when you look at it overall, both in terms  
24       of numbers of overdoses and in terms of magnitude  
25       of overdose.

26              There has been some degree of an effect  
27       across the population, but the magnitude of the  
28       effect is relatively minimal.



1                   And there's also the background  
2           information there, although the weight of evidence  
3           behind that information, in terms of switching to  
4           other overdoses and changes in -- whether the  
5           paracetamol changes is a change that's occurring  
6           on a population basis with other overdoses as  
7           well -- that sort of colors the interpretation of  
8           the impact of the legislation.

9                   But, you know, my reading of the  
10          literature from our literature review is that the  
11          overall impact of the legislation has been minimal  
12          to moderate at its greatest.

13                  DR. HAWTON:  Although -- if I can come  
14          back -- I mean, I would question, you know,  
15          whether a reduction of 30 percent, roughly, of  
16          liver unit -- you know, of liver transplants and  
17          liver unit admissions is sort of minimal.  It's  
18          quite a -- you know, has quite major economic as  
19          well as, you know, health outcome value, it would  
20          seem to me.

21                  DR. DARGAN:  Although I guess there are  
22          some studies that have shown an impact on  
23          hepatotoxicity in terms of liver transplant  
24          admissions, and some that have shown no impact.  
25          And so, looking at the data as a whole, although  
26          it's difficult to pull the data from the studies  
27          because of their different designs, potentially  
28          the impact is less, although I do agree with you,

1 Professor Hawton, that some of the studies have  
2 shown, you know, a significant impact of the order  
3 of 20 to 30 percent, but others have shown no  
4 impact.

5 DR. NELSON: Well, I'm glad that our  
6 colleagues from the United Kingdom see the  
7 daunting task we have before us to try to figure  
8 out what the best approach would be.

9 I think, at this point, we're going to  
10 say thank you, and a particular thank you for the  
11 traveling and for the time spent from our British  
12 colleagues, helping us here in the United States  
13 with this very difficult issue. So thank you  
14 both.

15 DR. HAWTON: Thank you. Bye.

16 DR. NELSON: We're now going to move on  
17 to the open public hearing.

18 Both the Food and Drug Administration and  
19 the public believe in a transparent process for  
20 information-gathering and decision-making. To  
21 ensure such transparency at the open public  
22 hearing session of the advisory committee meeting,  
23 FDA believes that it is important to understand  
24 the context of an individual's presentation.

25 For this reason, FDA encourages you, the  
26 open public hearing speaker, at the beginning of  
27 your written or oral statement, to advise the  
28 committee of any financial relationship that you

1 may have with the sponsor, its products and, if  
2 known, its direct competitors.

3 For example, this financial information  
4 may include the sponsor's payment of your travel,  
5 lodging or other expenses in connection with your  
6 attendance at this meeting.

7 Likewise, FDA encourages you, at the  
8 beginning of your statement, to advise the  
9 committee if you do not have any such financial  
10 relationships.

11 If you choose not to address this issue  
12 of financial relationships at the beginning of  
13 your statement, it will not preclude you from  
14 speaking.

15 The FDA and this committee place great  
16 importance in the open public hearing process.  
17 The insights and comments provided can help the  
18 agency and this committee in their consideration  
19 of the issues before them.

20 That said, in many instances and for many  
21 topics, there will be a great variety of opinions.  
22 One of our goals today is for this open public  
23 hearing to be conducted in a fair and open way  
24 where every participant is listened to carefully  
25 and treated with dignity, courtesy and respect.

26 Therefore, please speak only when  
27 recognized by the Chair. Thank you for your  
28 cooperation.

1                   The first speaker will be Dr. Anthony  
2           Temple.

3                   DR. TEMPLE: Good morning. My name is  
4           Anthony Temple. I'm a pediatrician, medical  
5           toxicologist, past president of the American  
6           Association of Poison Control Centers. I worked  
7           for McNeil for 20 years, retired in 2005. I  
8           consult in my retirement on a part-time basis,  
9           including with McNeil, and I flew here on my own  
10          ticket.

11                  I believe the most important labeling  
12          improvement that could be made now would be to add  
13          dosing instructions for children less than two  
14          years of age to the label. If that had already  
15          been done, the other pediatric issues would be of  
16          much less concern. This is at the heart of the  
17          product confusion and misdosing issue we've heard  
18          so much about.

19                  I was very surprised that the CDER  
20          working group recommended including dosing  
21          instructions for children under two years if  
22          accurate dosing can be determined and adequate  
23          efficacy data exists to support dosing. After a  
24          decade of review, are they still uncertain? If  
25          so, let me answer.

26                  Is it appropriate to put dosing for  
27          children less than two years on the label? Yes.

28                  Is there already a dosing schedule

1 appropriate for this age group with accurate  
2 dosing instructions? Yes.

3 Does adequate efficacy and safety data  
4 exist to support this dosing? Yes.

5 Pediatric acetaminophen products have  
6 been in use since 1955, and infants' drop in the  
7 exact same concentration for 50 years. And  
8 appropriate effective dosing -- pediatric dose for  
9 acetaminophen in the 10 to 15 milligram range has  
10 been established.

11 There is an age-related pediatric dosing  
12 schedule for acetaminophen, which uses  
13 appropriate, narrowly defined age ranges. This  
14 age-related schedule generally keeps the dose  
15 within the 10 to 15 milligram range. The median  
16 dose is somewhat lower for the youngest children  
17 and infants, and also for the smallest children  
18 for a given age, the dose may exceed 15 milligrams  
19 per kilogram in some circumstances, for example --  
20 and I don't know if I can point that out up there  
21 or not. Okay.

22 The dose proposed by FDA in the TFM,  
23 which is the same as in our schedule -- the dose  
24 is about 17 milligrams per kilogram, but that's  
25 not a problem. The schedule is more precise --  
26 I'm sorry. There's also a weight-related dosing  
27 schedule with specific weight ranges, and this  
28 schedule more precisely keeps the dose of

1       acetaminophen within the 10 to 15 milligram per  
2       kilogram range.

3               Both schedules have been in widespread  
4       use for nearly 25 years, and I'd venture to say  
5       that every pediatrician here has used them.

6               Numerous clinical trials have  
7       demonstrated the effectiveness of this dose in  
8       thousands of children. This slide shows data from  
9       12 unpublished clinical trials involving 688  
10      children receiving acetaminophen. The children in  
11      these trials ranged in age from six months to 11  
12      years. This slide shows data from another 20  
13      published clinical trials from which time course  
14      data could be extracted, and demonstrates the same  
15      effective pattern of antipyresis.

16              The largest pediatric drug trial ever  
17      conducted has demonstrated the safety of using  
18      this dose. The Boston University Fever Study  
19      evaluated serious adverse events resulting in  
20      hospitalizations for children administered  
21      acetaminophen or ibuprofen at two separate doses.

22              Among the 28,000-plus subjects given  
23      acetaminophen, 9,000-plus were in children under  
24      two years of age, and none of the acetaminophen  
25      participants had a serious adverse drug event  
26      which was hepatic in nature.

27              FDA's clinical review on the Nahata and  
28      Powell paper -- or comments on the Nahata and

1 Powell paper from 1984 -- they didn't mention that  
2 this paper provided data on children given doses  
3 90 milligrams per kilo per day, either as a 10 to  
4 15 milligram per kilo dose every four hours six  
5 times a day, or 24 to 30 milligrams per kilogram  
6 eight days -- every eight hours three times a day.  
7 And this study showed expected increases in peak  
8 plasma levels after three days' dosing, consistent  
9 with steady-state kinetics and no toxicity.

10 At an NDAC meeting in 1995, FDA asked for  
11 opinions about putting the dose on the label for  
12 children less than two years, and strong support  
13 was expressed by healthcare professionals for  
14 doing so.

15 In 1997, another NDAC meeting was held to  
16 review pediatric dosing. Panel members  
17 recommended doing so.

18 So in June 1998, McNeil submitted an SNDA  
19 for Children's Motrin ibuprofen and, in February  
20 1999 a citizens' petition for  
21 acetaminophen-containing products.

22 Within a few months, in April 1999, the  
23 FDA approved the SNDA for concentrated Motrin  
24 infants' drops, approving a dosing range for  
25 children 6 to 23 months, confirming that there is  
26 no reason not to have dosing information on the  
27 label for parents to use. That was ten years ago.

28 The response to the citizens' petition

1 did not proceed as expeditiously. And the  
2 difference in response to an SNDA and a citizens'  
3 petition is striking.

4 At a 2002 NDAC meeting held to review OTC  
5 analgesic labeling, FDA reported that the response  
6 to the citizens' petition had cleared the division  
7 and was being reviewed at higher levels in the  
8 agency, but unfortunately, since then, nothing has  
9 happened, and no substantive feedback has been  
10 provided, either to manufacturers or interest  
11 health professions.

12 The only response has been that we should  
13 check the regulatory calendar found in the unified  
14 agenda for proposed publication dates. Interested  
15 parties have regularly done so, only to see the  
16 proposed publication dates pushed back, and then  
17 pushed back again, and then dropped entirely from  
18 the agenda. And if you look at that list, it's  
19 just astounding.

20 And today you're being asked to vote on  
21 whether to have a single concentration liquid, and  
22 they haven't even tested the impact of label  
23 dosing.

24 For children less than two, there are no  
25 label dosing guidelines. Most often, dosing  
26 instructions are given verbally, but parents  
27 cannot confirm that dose for themselves by looking  
28 on the product label. If there is a



1 miscommunication or misunderstanding, there is no  
2 way to catch it without the dosing information.  
3 It's the labeling, not the concentration.

4 FDA has stated they are not aware of data  
5 indicating that already-implemented efforts have  
6 reduced the problem. So why hold back on the  
7 labeling? Inclusion of dosing information for  
8 children under two will help parents do the right  
9 thing and give the right dose for the right  
10 product, avoid the need to call the doctor, a  
11 friend or a relative for a dose, rely on recall,  
12 or just plain guess at the dose, and will affirm  
13 whether the dose given by the doctor or other  
14 healthcare professional is correct.

15 So, in conclusion, FDA must find a way to  
16 immediately approve acetaminophen dosing for  
17 children under two years. Just use the exact same  
18 pattern approved for ibuprofen products in 1999.  
19 But this is the most important thing.

20 In spite of whatever regulatory process  
21 needs to be followed, manufacturers should be  
22 granted permission to put dosing on the label  
23 immediately. At the conclusion of this hearing,  
24 they could make an announcement, and decouple from  
25 any pediatric issues. Let's do it now.

26 DR. NELSON: Thank you.

27 The next speaker is Thomas Clark.

28 MR. CLARK: Thank you for this

1 opportunity to address the committee. My name is  
2 Tom Clark. I'm director of clinical affairs for  
3 the American Society of Consultant Pharmacists and  
4 the ASCP Foundation.

5 The members of ASCP are pharmacists who  
6 provide services to older adults, including those  
7 who reside in long-term care settings, such as  
8 nursing homes, assisted living and a variety of  
9 other settings.

10 The focus of my comments will be kind of  
11 at the opposite end of the age spectrum. We've  
12 talked about pediatric and adult for most of the  
13 meeting over the last couple of days, but there  
14 has been very little attention or focus on older  
15 adults in particular.

16 One of the challenges with respect to  
17 acetaminophen, at least as far as what I've seen  
18 and heard over the last couple of days, is the  
19 lack of data on the demographics: Who is using  
20 acetaminophen? How much acetaminophen is used by  
21 older adults for chronic or persistent pain versus  
22 younger adults for acute pain? And I think, in  
23 terms of policy changes, it's important to look at  
24 acetaminophen policy in the overall context of  
25 pain management and not look just at acetaminophen  
26 in a silo, not look at just the potential adverse  
27 consequences in overdosing of acetaminophen in a  
28 silo, but think about potential for shifting of

1 patients to other medicines, NSAIDs,  
2 opiate-containing combination products and so on.

3 And this is particularly important when  
4 we look at the older adult population. Chronic  
5 pain is very common in older adults.  
6 Undertreatment of pain is persistent and  
7 widespread. Professional societies, like the  
8 American Geriatrics Society, and a number of  
9 others, recommend acetaminophen as first-line  
10 therapy for management of osteoarthritis and other  
11 forms of pain because the risks are relatively low  
12 in this population. From what I've seen about  
13 acute liver failure, it appears to be primarily in  
14 pediatric and younger adult populations, and it  
15 doesn't seem like older adults seem to have as  
16 much of a problem, based on what I've seen.

17 But at the same time, changes in policy  
18 could significantly impact access to acetaminophen  
19 by older adults. For example, studies done on  
20 osteoarthritis use a dose of acetaminophen of  
21 either 1,000-milligram every six hours or 625  
22 milligrams four times a day. Either way, you're  
23 talking about eight tablets a day of  
24 acetaminophen. That's 240 tablets a month. I  
25 cannot imagine how somebody could buy 32, you  
26 know, pills at a time and take 240 tablets a month  
27 for a chronic arthritis pain. Those types of  
28 package limitations would be very problematic for

1 older adults, particularly if blister-type  
2 packaging were used -- an older adult with visual  
3 impairment, cognitive impairment, Parkinson's  
4 disease, arthritis affecting the hands -- a number  
5 of health conditions can make it very difficult  
6 for older adults to be able to appropriately use  
7 that type of packaging.

8 And so these types of access issues for  
9 older adults should be considered in any kind of  
10 policy change that's being considered.

11 With respect to over-the-counter  
12 acetaminophen combination products, we would  
13 oppose eliminating over-the-counter combination  
14 products with acetaminophen, particularly because  
15 we would be concerned that NSAIDs might be the  
16 logical replacement.

17 Many older adults actually take either  
18 prescription or over-the-counter NSAIDs already on  
19 a regular basis for arthritis, and having  
20 additional NSAIDs and other OTC products might  
21 just shift the problem from acetaminophen to  
22 NSAIDs with respect to overuse -- unintentional  
23 overuse of other products.

24 We oppose also eliminating prescription  
25 acetaminophen combination products. We believe  
26 that these combination products containing opiates  
27 are especially important for people with moderate  
28 to severe pain, persistent pain. The lack of

1 hydrocodone as a single-ingredient product would  
2 be one issue.

3 We would support a elimination of  
4 propoxyphene-containing combination products, as  
5 well as propoxyphene itself from the market, but  
6 that's another discussion.

7 We do have concerns about unit-of-use  
8 packaging, as I mentioned earlier, limitation of  
9 medication for products that are used in the  
10 long-term care setting. If packages are limited  
11 to a blister-type package, it's very important  
12 that hospital pharmacies and long-term care  
13 pharmacies have the ability to continue to  
14 purchase bulk packaging because these pharmacies  
15 routinely repackage these products into a blister  
16 card, a unit dose, a pillow pack -- there's a  
17 variety of specialized packaging types that are  
18 used in these settings that are very  
19 patient-specific or institution-specific.

20 Pharmacies in these settings need the  
21 ability to purchase bulk supplies so that they  
22 can, you know, individually customize packaging  
23 for the facilities that they serve. So we would  
24 not want to see a blister pack be the only way  
25 some of these products are made available.

26 And with respect to unit-of-use for  
27 prescription products, one concern there is the  
28 potential for increase in pharmaceutical waste if

1       there are only designated quantity sizes  
2       available, prescribers may have to prescribe more  
3       tablets of opiate-containing products than the  
4       patient really needs in order to meet whatever the  
5       designated unit-of-use size is. And this could  
6       result in more waste, most potential for diversion  
7       and abuse of opiates when patients have leftover  
8       pills that they no longer need from dental  
9       procedures or whatever the case may be.

10               In summary, we do support public  
11       education related to acetaminophen, and we wish to  
12       highlight the need for additional research on  
13       acetaminophen in older adults, along with a  
14       variety of other medications, and we support those  
15       initiatives, so thank you for this opportunity to  
16       submit comments.

17               DR. NELSON: Thank you. The next  
18       presenter will be Pamela Snow.

19               MS. SNOW: Good morning, and thank you  
20       for inviting me and the Arthritis Foundation here  
21       today to give voice to the 46 million Americans  
22       with some form of arthritis. We are grateful for  
23       the increased public input into the FDA's  
24       evaluation and assessment of drugs used for the  
25       treatment of arthritis. We believe it is  
26       important for you to hear directly from people who  
27       use these drugs to relieve the often debilitating  
28       pain and inflammation of arthritis and related

1 diseases.

2 My name is Pam Snow, and I am one of the  
3 27 million Americans with osteoarthritis. I  
4 consider myself an active wife, mother and  
5 grandmother that refuses to allow the pain of  
6 arthritis to slow me down or control my life.

7 Seven years ago, at the age of 41, I was  
8 diagnosed with osteoarthritis in both knees. I  
9 have endured two knee surgeries, lots of physical  
10 therapy, and many hours of pain and pure  
11 discomfort. Today, I control my arthritis and my  
12 arthritis pain through a combination of positive  
13 outlook, physical activity, weight control and the  
14 occasional use of over-the-counter medications,  
15 such as acetaminophen.

16 I know, from experience, the important  
17 role of acetaminophen in relieving the pain of  
18 arthritis. I, for one, take it so that I can  
19 engage in physical activity and just to be active  
20 with my grandchildren.

21 The Arthritis Foundation serves as a  
22 resource for people with arthritis and provides  
23 them with knowledge to make better decisions.  
24 Acetaminophen is an important drug that helps many  
25 people manage their pain. However, we are well  
26 aware that some patients with arthritis frequently  
27 take acetaminophen in doses near the upper limit  
28 for safety to manage their pain.

1           If they then use another over-the-counter  
2           type medication for cold symptoms, for example,  
3           they can easily and unknowingly exceed the  
4           limitations and the safe dose levels and suffer  
5           liver damage.

6           Although we all hope that the clarified  
7           labeling regulations that went into place a few  
8           years ago would help limit or prevent this  
9           complication, it has not.

10          All medications have side effects, and  
11          these side effects are often related to dose. The  
12          Arthritis Foundation recognizes the importance of  
13          minimizing the risks of adverse effects from  
14          acetaminophen, but also wants the greater number  
15          of treatment alternatives available to people with  
16          arthritis -- from existing medications to new  
17          drugs to exercise and education programs and  
18          access to health professionals.

19          We believe that people with arthritis  
20          should have access to all beneficial medications  
21          as well as knowledge about their potential side  
22          effects so they can make a personal choice about  
23          the level of risk they are willing to accept to  
24          alleviate the daily pain of arthritis.

25          The continued concern over safety of  
26          arthritis pain relievers underscores the  
27          tremendous impact of arthritis on the nation and  
28          the need for ongoing research for development of



1 new medications, treatment and understanding of  
2 the disease.

3 We applaud the FDA's plan to expand  
4 educational programs for the public and health  
5 professionals regarding risk of overdose from  
6 acetaminophen and liver damage. We hope the  
7 public education will provide appropriate  
8 instructions to patients regarding the need for  
9 careful attention of how drugs, alcohol and even  
10 some food interact with each other and the way the  
11 body metabolizes acetaminophen.

12 It is important to all people with  
13 arthritis that any changes the FDA makes with  
14 regard to acetaminophen will not limit the  
15 availability of this important and generally safe  
16 drug, or increase its cost to the consumers. The  
17 challenge for people, like myself, with chronic  
18 arthritis pain is to assess the risks and benefits  
19 and costs of any treatment accurately.

20 I want to play an active role in  
21 decisions made about my treatment and I want to be  
22 given the opportunity to be fully informed about  
23 the effects and benefits associated with the  
24 treatment options as far as acetaminophen is  
25 concerned.

26 As the voice of 46 million Americans with  
27 doctor-diagnosed arthritis, I hope the FDA  
28 carefully considers the impact of your decisions

1 on the very people it is striving to protect.

2 In summary, the Arthritis Foundation  
3 believes, one, people with arthritis should have  
4 access to all beneficial medications, such as  
5 acetaminophen.

6 Two, the FDA and the pharmaceutical  
7 industry need to significantly increase patient  
8 education materials and appropriate warnings about  
9 side effects related to acetaminophen. It is all  
10 too important [sic] that this knowledge regarding  
11 serious side effects is lacking within the general  
12 population.

13 Consumers need to be made aware of the  
14 potential side effects so they can make a personal  
15 choice about the level of risk they are willing to  
16 accept to alleviate the daily impact and pain of  
17 arthritis.

18 The Arthritis Foundation is fully  
19 committed to working with the FDA and private  
20 industry to help communicate important information  
21 regarding the risks associated with acetaminophen.  
22 We look forward to working together to better  
23 inform the public about the appropriate use and  
24 doses regarding this important tool in the toolbox  
25 to treat arthritis.

26 The Arthritis Foundation also strongly  
27 encourages the FDA to consider including a  
28 consumer representative from the Arthritis

1 Foundation on future deliberations on this topic.  
2 Arthritis pain is one of the major reasons with  
3 use acetaminophen to relieve their daily pain.

4 Thank you for your time and  
5 consideration.

6 DR. NELSON: Thank you. The next  
7 presenter will be Carmen Catizone.

8 DR. CATIZONE: Thank you. Thank you for  
9 the opportunity to be here and meet with the  
10 advisory committees and share our thoughts from  
11 the State Boards of Pharmacy. I am the executive  
12 director of the National Association Boards of  
13 Pharmacy, the organization that represents all the  
14 state boards of pharmacy and jurisdictions that  
15 regular the practice of pharmacy, pharmacists,  
16 technicians, pharmacies and wholesalers in the  
17 United States, Canada, Australia, New Zealand,  
18 Guam and the Virgin Islands.

19 I, as an individual, and NABP as an  
20 organization, have no financial interests or  
21 conflicts of interest with any of the sponsors or  
22 manufacturers involved in this issue.

23 Today I'd like to focus my remarks on the  
24 prescription acetaminophen products and NSAIDs for  
25 labeling and dispensing and patient information,  
26 but also touch upon the over-the-counter products.

27 In 2004, when the state boards of  
28 pharmacy were approached by the FDA and requested

1 to require changes in the labeling of prescription  
2 products, the state boards of pharmacy agreed with  
3 the rationale, but could not implement the changes  
4 requested by the FDA. The reason behind the  
5 states' inability to make these changes was simply  
6 that they couldn't make changes for one drug. The  
7 states were concerned that additional changes  
8 would soon be necessary for other products, and  
9 that requirements for prescription labeling would  
10 soon be in a constant state of flux, and that  
11 labeling consistency and uniformity across the  
12 board would be lost.

13               However, much has changed since 2004.  
14 NABP recently commissioned a task force of experts  
15 and stakeholders to redesign a patient label with  
16 one overarching purpose and concern, to provide  
17 critical information to the patient so that he or  
18 she may use the medication appropriately and  
19 comply with the medication regimen. The label  
20 should be patient-centered. The label should not  
21 be used as an audit mechanism by third-party  
22 payers, nor should it be used for promotional  
23 purposes by dispensing pharmacies.

24               Further, the label should not be used as  
25 a sold means to determine compliance with pharmacy  
26 laws and regulations by pharmacy regulators. The  
27 prescription label cannot and should not replace  
28 clinical pharmacists' care responsibilities.

1           That purpose, and the work of the task  
2           force, directly responds to the request from the  
3           FDA in 2004 and the items under consideration by  
4           your advisory committee today.

5           The task force developed a new  
6           patient-centered prescription label, and with the  
7           approval of the NABP executive committee, is  
8           recommending states change their statutes and  
9           regulations to adopt this new label and this new  
10          requirement for all pharmacies and pharmacists.

11          Included in our recommendation to the  
12          states will be to redefine the prescription label  
13          and prohibit the use of any abbreviations for  
14          medications.

15          The data and information which the FDA  
16          has provided for acetaminophen will be used to  
17          substantiate the importance of such a request to  
18          the states.

19          That recommendation touches upon  
20          over-the-counter labeling and products as well.  
21          NABP believes firmly that the label for both the  
22          prescription product and over-the-counter products  
23          should be used as the primary vehicle to notify  
24          patients of the most critical information and most  
25          significant concerns. Additional guidance and  
26          educational information should be provided to the  
27          patient via the pharmacists and via alternate  
28          means that the patient will utilize and

1 understand.

2 NABP is asking the FDA to consider, in  
3 its final rules and current regulations regarding  
4 patient information initiatives, that they depart  
5 from the historic and current requirements of  
6 patient information sheets and the limited real  
7 estate of the prescription label and OTC labeling.

8 NABP would like to work with the FDA in  
9 our new program that we are launching to accredit  
10 pharmacy practice. In that program, we will  
11 develop standards that focus on patient safety,  
12 continuous quality improvement, and measurable and  
13 definable metrics for pharmacy practice.

14 As part of the program, we will be  
15 researching how patients receive and utilize  
16 information for their medications, both  
17 prescription and over-the-counter.

18 We believe that the advent of online  
19 resources and new methods for patients to receive  
20 information should be taken into consideration  
21 when deciding what labeling should be required on  
22 OTC packaging and prescription labels.

23 Our accreditation program will allow us  
24 to observe these situations using real-time  
25 practice data and real practice patients. The  
26 information will help us determine the most  
27 effective format and means to present information  
28 to patients.

1           The specific matter of acetaminophen and  
2           NSAIDs, both over-the-counter and prescription,  
3           will be a focus of our analysis, and the patient  
4           information we garner and the ways to present that  
5           information to patients will be something we will  
6           incorporate in our standards and the requirements  
7           for pharmacies to be accredited.

8           The analysis and the live practice  
9           setting through our accreditation program we hope  
10          will be extremely valuable and provide the  
11          opportunity to examine similar issues such as the  
12          risk, evaluation and mitigation strategies for  
13          opioids also under consideration by the FDA.

14          It is hoped that NABP can work with the  
15          FDA to establish and identify the appropriate  
16          balance for ensuring that the pharmacist provides  
17          patient care with the best resources available and  
18          the best means possible for the patient to  
19          maximize their medication use and avoid any  
20          adverse reactions. Thank you.

21          DR. NELSON: Thank you.

22          The next speaker will be Kevin Nicholson.

23          MR. NICHOLSON: Good morning, and thank  
24          you for the opportunity for me to speak today.  
25          I'm Kevin Nicholson, vice president and pharmacy  
26          advisor for the National Association of Chain Drug  
27          Stores. I am not aware of any financial  
28          disclosures that I should be noting at this time.

1           NACDS represents traditional drug stores,  
2           supermarkets and mass merchants with pharmacies.  
3           Our more than 170 chain members companies include  
4           regional chains with a minimum of four stores, to  
5           national companies. Our members fill more than  
6           2.5 billion prescriptions yearly, and we have  
7           annual sales of over \$750 billion.

8           As FDA recognizes in the background  
9           materials for the meeting, acetaminophen is an  
10          extremely safe medication when used at recommended  
11          doses. In addition, it is one of the most  
12          commonly used medications in the U.S. With this  
13          in mind, it is important to ensure that any new  
14          policies affecting availability of acetaminophen  
15          products are workable, considering a great  
16          consumer need for and widespread use of these  
17          products.

18          Placing unnecessary barriers to access  
19          would cause consumers to use other pain relievers  
20          and fever reducers that do not have the same  
21          highly reliable safety professor. As a threshold  
22          matter, we encourage FDA to renew efforts to  
23          educate consumers and healthcare professionals  
24          about the danger of liver toxicity associated with  
25          overdosing on acetaminophen and to encourage safe  
26          use practices. As you may be aware, NACDS is one  
27          of many stakeholders working with the Healthcare  
28          Consortium organized by the Consumer Healthcare



1 Products Association to develop a research and  
2 education program.

3 We would like to share our analysis of  
4 the options recommended by the acetaminophen  
5 working group.

6 We have concerns about requiring  
7 unit-of-use packaging for prescription  
8 acetaminophen products. Since many of the  
9 prescription products containing acetaminophen  
10 also contain narcotic pain relievers, we believe  
11 that unit-of-use packaging would have the  
12 unintended effect of causing more drug diversion  
13 and abuse among these products.

14 Since patients take pain medications for  
15 different purposes and different lengths of time,  
16 requiring unit-of-use packaging would require  
17 patients to purchase more doses of combination  
18 pain relievers containing acetaminophen and  
19 narcotics than they may need. Package sizes would  
20 be standardized, but patient needs are not  
21 standard. Unit-of-use packaging works for  
22 products that have a standard regimen or where the  
23 patient may have to be reminded to continue or  
24 complete the course of therapy, such as for oral  
25 contraceptives and antibiotics.

26 However, pain medications do not have a  
27 standard regimen, and we do not want to encourage  
28 patients to take more narcotics than they need.

1           With respect to requiring the pharmacy  
2           prescription label to identify acetaminophen as an  
3           active ingredient and not use different terms,  
4           such as APAP, we agree that there is room for  
5           improvement. However, a solution is not as easy  
6           as it might seem. The real estate on a  
7           prescription label is limited, and pharmacies are  
8           required by various state and federal laws and  
9           regulations to already include much information on  
10          prescription labels.

11          Spelling out acetaminophen on a  
12          prescription label may cause the font size to  
13          become so small as to be unreadable by some  
14          patients.

15          However, one potential solution would be  
16          for FDA to work with the Institute for Safe  
17          Medication Practices, ISMP, on initiatives to  
18          educate consumers and healthcare providers about  
19          the dangers of acetaminophen overdose. ISMP is  
20          the nation's only 501(c)(3) non-profit  
21          organization devoted to medication error  
22          prevention and safe medication use. ISMP may help  
23          FDA design recommended labeling to alert  
24          consumers -- it can help educate consumers that  
25          APAP and acetaminophen are the same chemical.

26          For example, FDA might consider working  
27          with ISMP to develop an auxiliary label that  
28          pharmacies can place on prescription bottles to

1 alert patients that their prescription medication  
2 contains acetaminophen.

3 Should FDA decide to require a medication  
4 guide for acetaminophen products, we urge FDA to  
5 consider the citizens' petition that pharmacy and  
6 consumer groups filed with the agency in 2008 to  
7 harmonize all consumers medication information  
8 into one useful succinct document.

9 FDA should work to make sure that  
10 patients receiving combination products do not  
11 have to also receive med guides. Med guides  
12 should be written for products, not for  
13 ingredients.

14 We advise against the option of  
15 eliminating combination OTC or prescription  
16 products that contain acetaminophen. As FDA has  
17 recognized, the available evidence indicates that  
18 OTC combination products are responsible for a  
19 relatively small percentage of acetaminophen  
20 overdoses. In addition, elimination of  
21 combination products would cause patients to take  
22 stronger narcotic pain relievers and would  
23 increase the use of non-steroidals, NSAID,  
24 products. Both outcomes would lead to increased  
25 adverse effects.

26 Elimination of combination OTC products  
27 would cause consumers to increase the use of  
28 combination OTC products containing aspirin or

1 NSAIDs, which could also lead to increased adverse  
2 effects.

3 Moreover, it is not clear that this would  
4 address the problem, as many consumers are not  
5 even aware that acetaminophen is a pain relieving  
6 agent in their combination products. In fact,  
7 they probably do not even realize that it is the  
8 active ingredient in many of the single active  
9 ingredient products that they take.

10 At a minimum, FDA should consider  
11 enhanced labeling or warning statements before  
12 considering eliminating these products.

13 FDA is also considering the options of  
14 limiting pediatric formulations to one  
15 concentration requiring the use of a measuring  
16 device and including dosing instructions for  
17 children under two years of age. If FDA decides  
18 to require the use of a measuring device, we would  
19 encourage FDA to standardize the measuring device  
20 and the concentration strength for pediatric  
21 products as well. Otherwise, parents may confuse  
22 which measuring device should be used with which  
23 product.

24 Moreover, we support the inclusion of  
25 dosing instructions for children under two years  
26 of age. Parents often seek healthcare providers'  
27 advice on how to dose acetaminophen for children  
28 under two. It would be ideal for parents and

1 healthcare providers to be able to follow FDA  
2 guidelines for this.

3 We ask FDA to move cautiously as you  
4 consider the options developed by the  
5 acetaminophen working group. We believe a high  
6 priority for FDA should be renewing efforts to  
7 educate consumers. We also ask FDA to consider  
8 the concerns I have mentioned about about the  
9 working group's proposed options. Thank you.

10 DR. NELSON: Thank you.

11 The next presenter will be John Sebbby.

12 MR. SEBBY: I'm John Sebbby with the  
13 National Pain Foundation, a non-profit dedicated  
14 to improving the quality of life for those living  
15 with pain through information, education and  
16 support. The NPF has received no funding for my  
17 presence here today.

18 The solution to balancing patient safety  
19 and patient access to care is patient education.  
20 The NPF recognizes acetaminophen as a safe and  
21 effective medicine for relieving pain and reducing  
22 fever when used as directed. We also know that  
23 too much acetaminophen may be dangerous if too  
24 much is ingested. We also know that education and  
25 awareness works.

26 Although I learned it when I was just a  
27 toddler, I still look both ways before I cross the  
28 street. Education works.

1                   After an effective awareness campaign  
2           earlier this month Utah Department of Health  
3           announced a 12.6 drop in unintentional  
4           prescription death last year compared to 2007, the  
5           largest drop in more than a decade, a result of an  
6           effective awareness campaign, Rx use only as  
7           directed and zero unintentional death.

8                   To better educate patients on their  
9           medications and treatment options, the NPF  
10          launched PainSafe, pain safety and access for  
11          everyone, and educational initiatives for  
12          patients, healthcare providers, pharmacists and  
13          the public to ensure the safe use of medications  
14          and other pain therapies for protecting access to  
15          care.

16                   The NPF supports the FDA's effort to  
17          improve the safe use of acetaminophen, one of the  
18          most widely used and safest medication available  
19          when used appropriately. the NPF, National Pain  
20          Foundation, believes it is extremely important for  
21          patients, providers to be aware of the cumulative  
22          amount of patients ingesting acetaminophen, as too  
23          much can be extremely dangerous. The NPF supports  
24          the efforts to support safety and awareness  
25          related to acetaminophen use.

26                   The National Pain Foundation supports  
27          patient education efforts that focus on safety.  
28          We support prominent labeling of risks of overdose

1 on packages of acetaminophen products. The  
2 National Pain Foundation supports changing all  
3 labels of products with acetaminophen to spell it  
4 out, and not use the APAP abbreviation.

5 The National Pain Foundation supports  
6 significant public and patient education efforts  
7 that include having a third-party independent  
8 non-profit organization manage the education, an  
9 ideal mediator between the FDA and industry.

10 The National Pain Foundation supports  
11 promoting healthcare professional education for  
12 physicians, pharmacists and other providers.

13 The National Pain Foundation opposes  
14 actions that limit patients' access to care. We  
15 oppose requiring the package of pills in blister  
16 packs. Blister packs can be very difficult to  
17 open for the elderly, those with arthritis and  
18 other ailments.

19 The National Pain Foundation opposes  
20 eliminating all OTC over-the-counter products that  
21 contain acetaminophen along with other ingredients  
22 for a combination product as it is more expensive  
23 to consumers and creates more packaging waste and  
24 is harmful to the environment.

25 The National Pain Foundation opposes  
26 limiting the number of pills in a bottle.  
27 Limiting the number of pills decreases access to  
28 pain relief to the 75 million Americans who suffer

1 from chronic pain and other illnesses.

2 This also increases the cost of patient  
3 health and creates more packaging waste and does  
4 not prevent consumers from buying multiple  
5 packages.

6 The National Pain Foundation opposes  
7 reducing the maximum recommended doses. Research  
8 indicates the current dosage is safe and is also  
9 the most optimum for best pain relief.

10 The National Pain Foundation strongly  
11 recommends patients always follow five tips for  
12 taking acetaminophen guidelines, that they do not  
13 exceed the recommended single dose and daily dose  
14 of acetaminophen, that they are aware that many  
15 over-the-counter prescription medications also  
16 contain a label APAP on prescriptions, that  
17 patients always calculate how much acetaminophen  
18 they are taking, especially to both  
19 over-the-counter and prescription medications, and  
20 be especially careful in calculating doses for  
21 infants and children.

22 Patients need to be aware that keeping  
23 acetaminophen products safely away from children  
24 and adults, and especially adults impaired  
25 thinking, and be aware that if you have chronic  
26 liver or kidney disease, consult with your  
27 healthcare provider before taking acetaminophen.

28 The National Pain Foundation believes



1       that a patient advocacy non-profit organization --  
2       efforts to promote safety and awareness related to  
3       the safe use of acetaminophen are needed to keep  
4       patients safe. And we believe that the greater  
5       patient public healthcare provider education  
6       efforts are the best tool to increase patient  
7       safety while maintaining access to care.

8               The National Pain Foundation believes  
9       that patient safety and access to care issues must  
10      be balanced to deal effectively with medication  
11      issues.

12             PainSafe provides solutions to help save  
13      lives and reduce injuries related to pain  
14      therapies while ensuring that pain care options  
15      remain accessible for everyone.

16             I thank you for allowing us to present  
17      our position on this important topic.

18             DR. NELSON: Thank you.

19             The next present will be Melissa Henry.

20             MS. HENRY: Good morning. Thank you for  
21      the opportunity to provide comments. I am Melissa  
22      Henry, director of regulatory affairs for  
23      Mallinkrodt, Inc., a Covidien company. Covidien  
24      has a long history as the world's largest producer  
25      of acetaminophen and the only North American and  
26      European manufacturer of the drug substance.

27             We sell bulk acetaminophen powder to  
28      other companies that manufacture prescription and

1 over-the-counter products. In addition, Covidien  
2 manufactures prescription combination products  
3 containing acetaminophen.

4 We support FDA's ongoing efforts to  
5 address patient safety issues related to  
6 acetaminophen. However, we believe any actions  
7 FDA may take should address root causes while  
8 maintaining patient access and reducing unintended  
9 adverse consequences. We offer the following  
10 comments.

11 Preserve acetaminophen's value for  
12 patients. As FDA has stated in its background for  
13 this meeting, the effectiveness of acetaminophen  
14 in relieving pain and fever is widely known. At  
15 recommended doses, it does not cause adverse  
16 effects such as stomach discomfort and bleeding.  
17 Therefore, it is critical to continue patient  
18 access to the unique safety advantages of this  
19 product while implementing appropriate educational  
20 measures.

21 Expand education and information to  
22 reduce risk. Covidien believes the FDA should  
23 focus on the root causes of this issue and expand  
24 the reach of the consumer educational campaign.  
25 FDA and industry should continue their  
26 collaboration to alert prescribers, dispensers and  
27 other healthcare professionals to the safety  
28 issues, providing guidance on how to communicate

1 this critical information to patients.

2 Repeated exposure to these messages and  
3 reliance on research to determine the  
4 communication's effectiveness will ensure patients  
5 understand these concerns and take steps to avoid  
6 them.

7 Covidien also supports expanding product  
8 labeling information to consistently identify  
9 acetaminophen in relevant products so patients can  
10 more easily identify the ingredient's presence.

11 Maintain availability of combination  
12 products. Covidien does not support eliminating  
13 combination products that contain acetaminophen,  
14 whether OTC or prescription. Doing so would  
15 adversely impact the ability of patients to access  
16 appropriate and affordable medications. It is  
17 particularly important that patients have an OTC  
18 option available, saving on healthcare costs by  
19 obtaining the drug without a prescription or  
20 physician's office visit.

21 The medical rationale behind combinations  
22 of acetaminophen and other prescription analgesics  
23 is the belief that combining a rapid-onset,  
24 short-acting agent with a slower-onset,  
25 rapid-acting drug will provide noticeable  
26 therapeutic benefit over use of either product  
27 alone.

28 Multi-modal pain relief provided by

1 combination prescription drug therapy may allow  
2 for reduced dosing of each analgesic, further  
3 reducing the risk of adverse events, while  
4 providing comparable or better analgesic relief  
5 than with either individual drug.

6 Fixed-dose combination ingredient  
7 prescription or OTC products are intended to  
8 reduce the likelihood of dosing errors. They  
9 eliminate the need for understanding and tracking  
10 multiple dosing instructions at potentially  
11 staggered intervals. Combination drugs also  
12 ensure use of the most appropriate ratio of one  
13 analgesic to another.

14 Recognize limitation of package size  
15 controls. Covidien agrees that package size  
16 limits should not be established for OTC products,  
17 given questions over their usefulness.  
18 Unit-of-use packaging for prescription combination  
19 drug products containing acetaminophen may be  
20 appropriate, but should not impair patient access  
21 to affordable pain management due to costly  
22 implementation requirements.

23 Avoid unintended consequences of changing  
24 dosing limits. When used as directed by the  
25 labeling, current acetaminophen OTC dosing limits  
26 have a well-established safety profile and  
27 extensive professional recommendations.

28 DR. NELSON: Thank you.

1           The final speaker in the open public  
2           hearing will be Dr. Rebecca Drake.

3           DR. DRAKE: Hi. Thank you. My name is  
4           Rebecca Drake, and I'm a pharmacist. Thank you  
5           for allowing me time to share my story. I have no  
6           financial disclosures.

7           Patient education needs to occur, but  
8           please consider labeling and packaging changes as  
9           well. My 24-year-old sister died from an  
10          unintentional overdose of acetaminophen which was  
11          taken over a period of only two weeks. A zany,  
12          outgoing and fun-loving young woman, she was  
13          preparing for her first trip abroad, our brother's  
14          wedding in Thailand. A few weeks before she left,  
15          she began experiencing significant acid reflux.  
16          Her doctor scheduled an EGD to be performed in  
17          about two weeks and, in the interim, she was  
18          started on a PPI and H2 blocker. Finally, she was  
19          told to take acetaminophen for the pain.

20          No one is sure how much acetaminophen she  
21          was taking each day, or if she was even told how  
22          much was too much, but before her EGD was  
23          performed, she awoke with acute abdominal pain.  
24          She was taken to a local ER where it was  
25          discovered that her LFTs were elevated to  
26          dangerous levels.

27          She was evacuated via helicopter to the  
28          nearest liver transplant center. Unfortunately,

1 her new liver proved to be too little, too late.  
2 The donor liver was unable to sufficiently reduce  
3 the toxicity in her blood, and she died of acute  
4 liver failure in November of 2008. She missed our  
5 brother's wedding, and we miss her dearly.

6 I'm a pharmacist. It was very hard to  
7 have my family ask me if I knew acetaminophen  
8 could do this, when I did. And I believe my  
9 family is above average in health literacy.  
10 However, this still happened to us. What about  
11 those families who aren't even literate, let alone  
12 health literate?

13 I learned yesterday that the largest  
14 percentage of patients with acetaminophen acute  
15 liver failure is young adults. Education alone  
16 won't work, especially in the young adult  
17 population who many times think they are  
18 invincible, don't know their own mortality and  
19 believe it won't happen to them. In addition, no  
20 part of the education that we saw yesterday seemed  
21 to target young adults.

22 I believe drastic measures need to be  
23 taken to protect consumers, and I don't believe  
24 public education will be enough, or the tiny  
25 printed addition to the label that was just added.

26 I recommend implementing chunking on  
27 labels. However, since most patients don't always  
28 read the label, additional actions are needed.

1           My family is now aware of the dangers of  
2           acetaminophen, perhaps too aware because some  
3           state they will never take it again. However, I  
4           would not be surprised if they unknowingly took  
5           acetaminophen in an OTC combination product for  
6           their last cough or cold.

7           Thank you for your time.

8           DR. NELSON: Thank you.

9           The open public hearing portion of this  
10          meeting has now concluded and we will no longer  
11          take comments from the audience. The committee  
12          will now turn its attention to address the task at  
13          hand, the careful consideration of the data before  
14          the committee as well as the public comments.

15          I guess our first order of business,  
16          we're going to take a break. We will be back in  
17          about 15 minutes. I will remind the committee  
18          members not to discuss issues with each other  
19          during the break.

20          (A recess was taken.)

21          DR. NELSON: Okay. We're going to get  
22          restarted, if people can retake their seats.

23          Okay. So we're getting to the meat and  
24          potatoes part of our meeting, but before we jump  
25          into our discussions and the chance for everybody  
26          to express their opinion -- and I know many of you  
27          have been champing at the bit to do that -- we're  
28          going to have a presentation of the options and

1 questions that we're supposed to be reflecting  
2 upon as we move forward.

3 So Dr. Susan Johnson, the associate  
4 director of ONP, is going to present us with these  
5 issues that we have to think about.

6 DR. JOHNSON: Thank you, Dr. Nelson.  
7 Good morning. My name is Sue Johnson. I'm the  
8 associate director of the Office of  
9 Nonprescription Products. I'm the last leg of the  
10 presentation relay before we get to the most  
11 important part of the meeting, and that is the  
12 committee's deliberations. I'm sure we're all  
13 anxious to hear your comments.

14 I'm going to take a few minutes before we  
15 go there, there, to go over the questions that we  
16 have for the committee to address about our  
17 options for public health interventions.

18 We understand that there is incomplete  
19 information about the acetaminophen liver injury  
20 problem, and there are specific data that we would  
21 all like to have that we don't have, in various  
22 areas, I'm sure.

23 So what we're asking the committee to do  
24 is to take on the very difficult task which you  
25 alluded to earlier, to help the FDA construct a  
26 rational approach to risk minimization.

27 FDA's current view is that acetaminophen  
28 is an effective drug that can be used to treat



1 pain and fever in appropriate populations. We  
2 believe that conditions can be defined for  
3 acetaminophen to be used safely and effectively.

4 And while we recognize that there can be  
5 multiple interpretations of the existing data, we  
6 believe this problem warrants additional action.

7 Internally, we've created recommendations  
8 that you saw in the work group background  
9 document. There is no a complete consensus on  
10 many of the recommendations internally at FDA,  
11 although some have achieved consensus and are  
12 presented that way in the document.

13 We also want to highlight the recent  
14 publication of the final rule for OTC products  
15 that provides consumers with more safety  
16 information.

17 We have ongoing educational efforts that  
18 we believe are an important component in solving  
19 this problem. But the messages that need to be  
20 received by acetaminophen users are relatively  
21 complex, and we need to know that achieving this  
22 kind of goal can be done through multiple types of  
23 interventions -- I'm sorry. We believe that  
24 achieving this goal can be done through multiple  
25 interventions.

26 Based on precedent -- and this is not  
27 targeted at any particular industry or segment of  
28 the industry. Based on precedent, this situation

1       probably is insufficient -- I'm sorry -- is  
2       unlikely to be sufficiently managed through  
3       education alone.

4               So we're here to gather the perspectives  
5       of the advisory committee and the public before we  
6       select or implement additional interventions.

7               This diagram is offered as a summative  
8       model of the many facets of what we've heard about  
9       liver injury. We heard yesterday about the  
10      widespread use of acetaminophen products and the  
11      basis for acetaminophen's dose-dependent toxicity.  
12      This seems to point us towards a predictable  
13      occurrence of misdosing and toxicity.

14              We have seen epidemiologic data of this  
15      toxicity from both FDA and our industry  
16      colleagues, so I've borrowed the pyramid event  
17      descriptor from Dr. Lee and Dr. Budnitz, and have  
18      placed the event data at the center of our  
19      understanding.

20              From these data, we can characterize, at  
21      least to some extent, the affected patient  
22      population. Further, we can look at the types of  
23      products and the extent of exposure to which the  
24      various events can be attributed. And, finally,  
25      we can consider making changes, through FDA, CDC,  
26      industry, healthcare provider interventions and  
27      interventions on the parts of others to improve  
28      the environment in which acetaminophen products

1 are used.

2 The data do not yet completely provide us  
3 with explicit links among these factors, but I'll  
4 list some of the considerations for the various  
5 components of this model.

6 With regard to the observed events, the  
7 committee will need to consider the source of the  
8 data -- the various sources of data about which  
9 you heard yesterday and the characterization of  
10 the cases from each source. The limitations of  
11 the various data sources were made explicit for  
12 some of these sources, but the ability to  
13 understand severity, outcomes and causal  
14 associations with acetaminophen dosing affect the  
15 committee's ability to draw conclusions.

16 Ultimately, these events provide a  
17 foundational assessment of the overall magnitude  
18 of the problem. You may assess magnitude in terms  
19 of absolute number of events, or you may factor in  
20 other considerations, such as how tolerable the  
21 problem is to you.

22 And when we begin to look at the  
23 magnitude of the problem, we're faced with  
24 differences amongst various patient groups. We  
25 can see differences based on the type of pain  
26 being treated, patient age, liver function --  
27 which is influenced by a number of known and  
28 unknown factors -- the purposefulness of misdosing

1 events, and what patients know about acetaminophen  
2 use.

3 The events and our assessment of the  
4 magnitude of the problem also differ by factors  
5 related to the drug products involved. We may  
6 reach different conclusions about intervention  
7 options based on drug dose, duration of treatment,  
8 regulatory status, product formulation or access  
9 considerations.

10 And the events tell us about the backdrop  
11 for acetaminophen use. For instance, they suggest  
12 ways that both public and private interests could  
13 have different roles in acetaminophen use by  
14 modifying important use environment factors, like  
15 labeling, packaging, education and research.

16 And I'll mention here that while we don't  
17 have time for an extensive discussion at this  
18 meeting, FDA is very aware of the need to  
19 operationalize any interventions, together with a  
20 plan for monitoring the impact of that  
21 intervention. And we heard that need reinforced  
22 in the discussion yesterday.

23 Next I'm going to walk through the format  
24 of the intervention options that we've identified  
25 for you to consider, and the questions that we're  
26 posing about those options.

27 You all have a yellow handout with the  
28 questions in your packets, and you may want to

1 pull that out now.

2 The options on which the questions are  
3 based today have been modified a bit from the  
4 options backgrounder that you received to make  
5 this meeting more manageable. We didn't want to  
6 keep you here till next week, so we had to amend  
7 some of the way that they were presented in the  
8 options backgrounder. And you'll see that they're  
9 no longer in the order -- the same numerical order  
10 that they were in in the options backgrounder.

11 If you first look at the last page of  
12 your handout, page 9, you'll see a list of general  
13 considerations. These considerations are the  
14 items that we hope that you will use when  
15 evaluating each option, including things like the  
16 potential impact of the option to decrease liver  
17 injury, and some of the practical aspects of  
18 implementing the option.

19 So you may want to tear off this page now  
20 so you can use it as a reference as you go through  
21 each of the options.

22 Next, if you'll turn to page 2 of the  
23 handout, we'll use the first option as an example.  
24 You can first see the option listed in the box.  
25 Under the box you can see specific considerations  
26 related to this option. Please think about these  
27 specific considerations as well as the general  
28 considerations when addressing each option.

1           Then under the specific considerations,  
2           you can see the actual questions posed to the  
3           committee that you'll be voting on. The response  
4           choices for questions 1 through 9 are the same,  
5           and you'll use the electronic devices at your seat  
6           to vote. The electronic devices will be further  
7           explain a little later.

8           The response choices include A, B and C,  
9           so if you do not recommend the option, choose  
10          option C. If you recommend the option, choose  
11          option B. And if you recommend the option and  
12          believe that that option should be implemented as  
13          a high priority, choose option A.

14          This format is intended to help FDA  
15          understand how strongly you feel about the  
16          implementation of each option. So what you have  
17          is an option, general considerations, specific  
18          considerations, specific questions, and the  
19          response choices.

20          Now we'll walk quickly through the  
21          options. We ask you to consider your responses to  
22          the individual questions. In addition, be mindful  
23          of how the options may fit into an overall risk  
24          minimization plan and the potential for synergies  
25          among the named options or other options that you  
26          may want to articulate.

27          We have divided into those focused on  
28          nonprescription products and those focused on

1       prescription products.

2               The first option takes into consideration  
3       the generally predictable relationship between  
4       dose and exposure to acetaminophen and the extent  
5       of liver injury. The option is to lower the  
6       maximum total daily dose, single dose, the dose  
7       increment or tablet strength, or a combination of  
8       these. This option is to understand whether you  
9       believe that such changes could lead, in the  
10      actual use setting, to a functional increase in  
11      the protective gap between safe exposure and toxic  
12      exposure.

13              Here you will want to consider the  
14      dose-response data presented yesterday to  
15      determine if the efficacy associated with the  
16      higher doses is sufficiently greater than for the  
17      lower doses to justify and increased safety  
18      concerns.

19              The next option links to the previous  
20      one. It asks, in the case that the OTC is  
21      lowered, whether a higher dose should be retained  
22      as a prescription product. The need for access to  
23      the higher doses is at issue in this option.

24              Option 1b, this option, can be enacted  
25      only in associated with a change in 1a, but 1a may  
26      be enacted alone.

27              At the next option, we want to recognize  
28      Dr. Hawton and Dr. Dargan's perspectives about

1 making the changes to limit pack size of  
2 acetaminophen in the U.K. marketplace. We'd like  
3 the committee to offer their thoughts on how this  
4 experience may translate to the U.S. marketplace.

5 While this intervention is largely  
6 targeted at those who intentionally act to bring  
7 about self-harm, the committee may also see a role  
8 for it in helping to change the public perception  
9 of the overall safety of acetaminophen products.

10 The next option is to eliminate OTC  
11 combination. For this option and for the next  
12 option, limiting liquid OTC formulations, the  
13 magnitude of the specific problem and the  
14 likelihood that the problem is amenable to change  
15 may both be important considerations.

16 Now we'll turn to the options proposed  
17 for prescription products. This is perhaps the  
18 most controversial of the proposed options. Some  
19 have voiced publicly the logical argument that the  
20 only way to ensure a decline in  
21 acetaminophen-related liver injury associated with  
22 prescription products is to eliminate the  
23 prescription combination products. Others contend  
24 that there is a potential to introduce other  
25 significant drug safety and public health  
26 considerations by changing the stable of available  
27 products for pain treatment.

28 Option 3 is to implement unit-of-use



1 packaging associated with warning, ingredient  
2 identification and a medication guide. As with  
3 the recent final rule for OTCs, we think that  
4 standardizing the material that is prominent on  
5 the package can have benefit.

6 Option 4 is to implement a boxed warning  
7 in package inserts. This is largely intended to  
8 elevate the toxicity in the minds of prescribers,  
9 but it may also carry over to a medication guide,  
10 if there is one.

11 Options 3 and 4 do not need to be  
12 implemented together.

13 Question 10, then, is to further assess  
14 your prioritization preferences and help FDA  
15 understand how best to use our resources to take  
16 action. You have heard some about the next steps  
17 needed to implement changes for NDA products and  
18 for the OTC monograph, and recognize that  
19 implementation of any of the interventions will  
20 take some time.

21 So you will be asked, at the last break  
22 of the day, to fill out a paper ballot to indicate  
23 your highest priority option.

24 Finally, in question 11, we'd like to  
25 hear your thoughts about interventions that have  
26 not been named as options.

27 On behalf of the FDA, I'd like to thank  
28 the committee for your service and will leave you

1 to your deliberations. We are available to  
2 address any questions that arise, and I'll turn  
3 the floor back to Dr. Nelson.

4 DR. NELSON: Thank you.

5 Okay. Between now and lunch we are going  
6 to have some discussion, finally. I'm sure  
7 everybody is happy about that. For the next 20  
8 minutes or so, I'd like to do something a little  
9 bit different than discussing the individual  
10 options. I'd like to take that time to allow the  
11 committee to discuss amongst itself internally  
12 some of the high-level public health issues that  
13 we really haven't had a chance to discuss up to  
14 this point.

15 Many people are waiting to ask questions  
16 of the sponsors and of the FDA. And what I was  
17 hoping was that you could turn those questions  
18 into comments or internal questions that could be  
19 used to benefit the committee as a whole.

20 I would also ask if we could keep those  
21 questions to this more global concept, things  
22 about, you know, education or risk assessment  
23 rather than, you know, going into the details  
24 about the individual options and voting items that  
25 we're going to discuss in a short period of time.

26 When we get to the actual vote or the  
27 discussions, we have somewhere on the order of 20  
28 minutes or so per question to have a discussion

1 before we actually vote. So there will be some  
2 time to discuss the minutia about those individual  
3 questions. So I would like to keep this  
4 discussion to about 20 minutes, and I'd like to  
5 see if anybody has any comments or issues to bring  
6 up at this point.

7 I will start with Dr. Kramer.

8 DR. KRAMER: Actually, I gave some  
9 thought last night, after yesterday's session, and  
10 having read all the background materials, I think  
11 it's very important for us to talk among ourselves  
12 here because I think we have -- I just have said  
13 my name, Judith Kramer -- a heavy responsibility  
14 on the committee. This isn't the usual sort of  
15 advisory committee where we're trying to sort out  
16 if a signal is real. We actually have a  
17 substantial numbers of fatalities that are  
18 occurring, and at least the data suggest that many  
19 of them are unintentional.

20 So I just wanted to say that, you know,  
21 if we step way back, it's really striking that  
22 situations where safety concerns develop slowly or  
23 become -- we become aware of safety concerns  
24 slowly over a number of years are particularly  
25 dangerous.

26 I was thinking yesterday of a story I was  
27 told -- I actually don't know if it's true -- but  
28 the story about if you drop a frog in boiling

1 water, it will jump out, but if you put him in  
2 water and turn the heat up slowly, it will stay  
3 there till it dies. And I was thinking about that  
4 vis-a-vis where we are today with acetaminophen.  
5 If we knew everything we know now and we were  
6 looking at what's the best way to market and  
7 package this, we would have a different situation.

8 But over the years, really through no  
9 one's fault, because we assumed safety, we've gone  
10 through this situation where we shifted from the  
11 availability of a 325-milligram tablet as the most  
12 commonly used product to maybe an Extra Strength  
13 occasionally available, to almost a complete  
14 substitution; it's hard to find 325 milligrams on  
15 the shelf now, because it's completely dominated  
16 by a higher dosage strength, without, at least  
17 from my observation from yesterday's discussion,  
18 not a clear-cut demonstration that that's going to  
19 make a difference in terms of the kind of mild to  
20 moderate pain that most patients use it for  
21 over-the-counter.

22 And, similarly, assuming safety, we've  
23 included it in so many over-the-counter products  
24 with the idea of, you know, maybe having better  
25 compliance to the right dose for each individual  
26 product, but compounding the problem of  
27 unintentional overdose.

28 And then our assumption of safety

1 relative to NSAIDs made us bill this as a safe  
2 drug with the unintentional effect of making it  
3 hard to convince patients that there are  
4 situations where it could be really unsafe.

5 So one of the observations I want to  
6 share with the committee -- and this is just my  
7 thinking about this -- is that if we step back  
8 away from the individual questions, many of the  
9 recommendations place the burden of responsibility  
10 directly on the patients. Actually, that's what  
11 education does.

12 And through my own experience in trying  
13 to focus on education to improve adherence to  
14 life-saving medications, the actual data showing  
15 effectiveness of educational efforts alone is not  
16 very encouraging here. And I was really struck  
17 when I read the National Pain Foundation's  
18 comments in the backup material -- and I think it  
19 was repeated again today -- their words to  
20 patients are, quote, it's up to you to calculate  
21 how much acetaminophen you're taking.

22 And I think that is quite a tall order,  
23 given what we know about patient literacy, the  
24 way -- even if we had the perfect labeling, we're  
25 putting all the safety issues on patients.

26 So I'd like to raise a consideration  
27 among ourselves that we should think about, with  
28 each option, whether it engineers in safety

1 because most safety experts tell you if you want  
2 something to be safe, you have to engineer it into  
3 the system.

4 And as one of the public speakers said  
5 yesterday, does it really make sense to combine a  
6 highly addictive drug, like hydroxycodone [sic]  
7 and oxycodone, with a dose-related hepatotoxin  
8 when we know that chronic pain patients tend to  
9 escalate their dose of opioids for pain relief,  
10 and many times inadvertently increasing to a toxic  
11 dose of acetaminophen, as an example.

12 But that general question, does the  
13 solution engineer in safety, is one I think we  
14 should consider.

15 And, finally, I want to say that there is  
16 an elephant in the room that we really should talk  
17 about explicitly instead of having it act on what  
18 recommendations people make, and that is that  
19 there are tremendous -- given the slow realization  
20 of the safety concern here, there are tremendous  
21 cost and commercial implications to some of the  
22 recommended changes.

23 Any change in dosage form or removal of  
24 combinations would have enormously negative  
25 commercial implications. For instance, if we  
26 reduce the tablet size from 500 to 325, that would  
27 essentially mean most oral dosage forms, OTC,  
28 would have to be removed from the market.

1                   And I think that the FDA's experience in  
2                   retail outlets being reluctant to deliver bad news  
3                   about a product they're trying to sell is  
4                   instructive.

5                   And the reason I mention this elephant in  
6                   the room is that I think if -- we need to talk  
7                   about it explicitly among ourselves because,  
8                   otherwise, these conditions frequently can  
9                   overshadow the public health considerations. And  
10                  I think that we can't let that happen.

11                  So I personally think that our very --  
12                  snail's pace of progress over the last two decades  
13                  to address this public health problem is really,  
14                  if we step back, not very acceptable, and I would  
15                  like to encourage us to think about engineering in  
16                  safety rather than expecting patients, who are the  
17                  victims of this problem, to figure it out and fix  
18                  it.

19                  Thanks for the chance to express I know  
20                  some of which is opinion, but my observations.  
21                  Thanks.

22                  DR. NELSON: Thank you.

23                  Dr. Levine.

24                  DR. LEVINE: Thank you. I actually want  
25                  to talk a little bit about safety, too,  
26                  indirectly, and it relates to alcohol. I have  
27                  concerns about the warning, current warning, about  
28                  three alcoholic drinks as being -- no more than

1 three alcoholic drinks. I think these are mostly  
2 female patients who metabolize alcohol in a  
3 different way than males.

4 The second thing is three is far too  
5 much. If you work in a liver study unit like I  
6 do, and you ask some of our patients how many  
7 beers they're having, they'll tell you, I have two  
8 or four glasses of beer.

9 When you ask them about the beer, it  
10 turns out that about 20 percent are having  
11 24-ounce bottles of beer, not 12-ounce bottles of  
12 beer.

13 But my question is first to Dr. Dargan,  
14 briefly, and perhaps you can shed a little  
15 information on whether the warning label, if there  
16 is a warning label in the U.K. -- if there is one,  
17 I'd like to know what the rationale is for that,  
18 and if there's not, why not, and what's the  
19 rationale for not having a label.

20 DR. NELSON: Just before you answer, what  
21 I would like, Paul, and the others, is if we can  
22 keep our answers our brief as possible. I know we  
23 try to do that generally, but it's particularly  
24 important now.

25 DR. DARGAN: I'll be very brief. There  
26 is no specific mention of alcohol at all on the  
27 U.K. pack currently, and the -- unfortunately, I  
28 don't have the wording, you know, verbatim here,



1 but it is along the lines of paracetamol can cause  
2 liver damage in excessive doses. I mean, I'm  
3 paraphrasing what it says, but it's something  
4 along those lines that's on the package, but it  
5 currently doesn't have information regarding  
6 ethanol or alcohol.

7 DR. LEVINE: Thank you. Well, since we  
8 don't know precisely what dose of alcohol causes  
9 concomitant toxicity with paracetamol, but we do  
10 know that there's certainly epidemiological  
11 evidence -- and we know from Hong Kong, by a paper  
12 by Chan a long time ago, clearly showed that  
13 people ingesting just as much acetaminophen in  
14 Hong Kong have much less toxicity because they  
15 have a much lower drinking.

16 I think the label should be considered as  
17 low as low can be, and possibly saying there  
18 should be no alcohol concomitant with  
19 acetaminophen. That's my comment.

20 DR. NELSON: Thank you.

21 Dr. Farber.

22 DR. FARBER: Thanks very much. Neil  
23 Farber, UC San Diego. I had two questions from  
24 yesterday, and actually I can do as you suggested  
25 and turn them into comments.

26 I'd first of all like to expand on the  
27 issue about education and labeling as has been  
28 advocated by some individuals to be the sole

1 method of trying to address this problem. I think  
2 we have sufficient data to say that education  
3 alone is not going to be sufficient. And I think  
4 there's a really good reason for this.

5 If one looks at a learning model in terms  
6 of patients, learning has to have three  
7 components. One is knowledge, which is what has  
8 been addressed by the FDA as well as by  
9 manufacturers. But there are two other components  
10 that any kind of learning has to have, and that is  
11 basically an attitudinal shift and a skill set.

12 The attitudinal shift is going to be one  
13 that would be very, very challenging, I believe,  
14 in this country.

15 We've heard time and time again during  
16 the last two days that acetaminophen is a, quote,  
17 safe and effective drug when used as directed.  
18 Patients generally will hear safe and effective  
19 and don't hear the rest. So that the attitude is,  
20 I don't need to do any of the looking at labels,  
21 et cetera, et cetera, because it's safe; it's not  
22 going to harm me. And the knowledge that it's not  
23 safe if used inappropriately may not penetrate.

24 So I think that -- basically I agree that  
25 we need to engineer in some safety measures.

26 In addition, the skill set requires more  
27 than just education and attitude shift; it  
28 requires training patients and individuals who

1 take acetaminophen to use it correctly, and that's  
2 something that's very intensive.

3 If, on the other hand, one looks at a  
4 behavioral model -- note that this is a behavior  
5 that people take acetaminophen and don't look at  
6 the labels, et cetera, then we're talking about an  
7 even greater intensive effort, one, for example,  
8 like a Prochaska model in which one has to have a  
9 one-on-one intervention in training people to sort  
10 of make this behavioral change, and it's over a  
11 period of time, and it's intensive. I don't think  
12 we have the resources to be able to do that.

13 So I think more needs to be done, and I  
14 think the committee needs to think about that when  
15 they're addressing these issues.

16 The second issue I would address would  
17 be, basically, where can we make our greatest  
18 impact? And I think one of the things that we  
19 need to think about is that a greater impact, I  
20 think, can be made on unintentional overdoses  
21 rather than an intentional overdose.

22 Basically, with an intentional overdose,  
23 yes, it's impulsive; yes, people can do some  
24 things. But I think we've seen from the U.K. data  
25 that it's not going to make a major difference in  
26 terms of what we do.

27 People, if they are bound and determined  
28 to commit suicide, will do so no matter what we do

1 in terms of changing the drugs that are out there.

2 On the other hand, unintentional  
3 overdoses are something that we can address and is  
4 half of the deaths that occur in this country,  
5 half of the emergency room visits in this country,  
6 half of the liver transplantations in this  
7 country. So I think we need to think about that.

8 One aspect I'm particularly concerned  
9 about would be the issue of combination opioids  
10 and acetaminophen which, as has been pointed out,  
11 is something that is likely to occur because  
12 patients gain tolerance to short-acting opioids  
13 and start using more and more and, therefore, more  
14 and more acetaminophen.

15 I would like to know, from Dr. Filie --  
16 and I hope I pronounced her name right -- if she's  
17 here, are there any data to show that hydrocodone  
18 alone is less effective than the combination of  
19 hydrocodone and acetaminophen? Not the fact that  
20 there are less emergency room visits for  
21 hydrocodone than the other agents, but  
22 specifically hydrocodone versus hydrocodone and  
23 acetaminophen.

24 So is it less effective? Are there less  
25 side effects? Is hydrocodone less abused in  
26 comparison between the two -- that is, hydrocodone  
27 alone versus hydrocodone plus opioids [sic]?  
28 Because, in fact, if those data are not available,

1 then we have to think about the fact, are there  
2 really differences? If there aren't, then why are  
3 using the combination of hydrocodone and  
4 acetaminophen?

5 DR. HERTZ: I don't see Dr. Filie here,  
6 but I can answer -- this is Sharon Hertz over here  
7 from FDA. I work with Dr. Filie.

8 We have no approved single-entity  
9 hydrocodone products on the market, so comparative  
10 data with regard to abusability is not available.

11 There is a bit of literature -- there are  
12 a few papers available. There's not a lot to look  
13 at the effects of the combination. But in the  
14 limited studies there are, there is improved  
15 efficacy for the combination over the individual  
16 components. And I'm trying to remember the doses  
17 that were studied. It was a gram of acetaminophen  
18 and I want to say, but I could be off, 10  
19 milligrams of hydrocodone.

20 So that, to a limited extent, does exist  
21 in the literature. And I'm trying to remember the  
22 rest of the levels of question in your --

23 DR. FARBER: If there's any data on  
24 differences of abuse --

25 DR. HERTZ: So because --

26 DR. FARBER: -- or side effects.

27 DR. HERTZ: Right. So because there's no  
28 single-agent hydrocodone available, we have no

1 data on the abuse, and that's why you saw, for  
2 instance, in the prescription data and the DAWN  
3 data, anything that said hydrocodone was in  
4 combination.

5 In terms of side effects, the studies  
6 that are available in the literature are  
7 short-term studies, and they really were focused  
8 on efficacy, so we don't have information on  
9 safety.

10 DR. NELSON: Thank you. Dr. Shrank.

11 DR. SHRANK: Thanks. This is more of a  
12 question for the FDA. One of the issues that's  
13 come up a lot has to do with considering what will  
14 happen in terms of switching to NSAIDs, and I  
15 think everybody at this table recognizes that  
16 there's lots of important implications with  
17 respect to switching to NSAIDs.

18 That said, it's kind of a paralyzing, or  
19 a circular problem, because I think many of us  
20 would argue that better education or warnings are  
21 necessary for NSAIDs as well. And we could easily  
22 envision us acting less now and then, in 18 months  
23 or a year, talking about NSAIDs and saying, well,  
24 what about if people are going to be switching to  
25 acetaminophen?

26 So -- my sense is that I would hope that  
27 that wouldn't be paralyzing to this group. And I  
28 wanted just sort of some more guidance from you

1 all about how to think about that issue.

2 DR. HERTZ: Well, within the therapeutic  
3 range I think we've seen that there's not a lot of  
4 toxicity due to the acetaminophen. Most of the  
5 toxicity that we are concerned about with the  
6 NSAIDs is well within the therapeutic range. So  
7 while we worry about the inadvertent use of too  
8 much acetaminophen, particularly in the  
9 prescription products, that's where the toxicity  
10 lies, and that's why I think that, overall, the  
11 numbers aren't huge. They're important, but  
12 they're not huge.

13 The toxicity that we see with the NSAIDs  
14 occurs within the therapeutic range, and I think  
15 that's why, depending on whichever estimate you  
16 choose to look at, if you look at the article by  
17 Fries -- there's another article that Dr. Filie  
18 cited -- the numbers are still present, so that's  
19 the consideration.

20 We can label the NSAIDs however we want.  
21 The toxicity occurs in the therapeutic range and  
22 even, to some extent, in the OTC range, although  
23 presumably less.

24 DR. NELSON: Dr. Vaida?

25 DR. VAIDA: I just want to comment for a  
26 minute here -- and maybe it's a follow-up with  
27 what Dr. Kramer tried to give a visual.

28 I had sent this to Elaine last week when

1 I started going through the material, and ISMP,  
2 when we, for the last probably 20 years, when we  
3 go through our error data and try to come up with  
4 recommendations, this is what we always look at.  
5 And this is what we call our rank order.

6 And I just think, for the committee, this  
7 is probably something that may be helpful for us  
8 to think about. And what you can see is on the  
9 bottom here is education, and it's very important,  
10 but it's not long-lasting. You have to keep doing  
11 it. And we heard a lot about education. So you  
12 have to move up -- you have to standardize and you  
13 have to put in constraints.

14 And I just think it's some of the things  
15 that may be helpful if we refer back to something  
16 like this and think, this is the way that you try  
17 to engineer harm out of the system -- and it's  
18 what we do, as an organization, whenever we try to  
19 come up with recommendations.

20 DR. NELSON: Thank you.

21 Dr. Stergachis.

22 DR. STERGACHIS: Thank you. I just  
23 wanted to share an observation that I think  
24 there's been very little discussion of the  
25 populations that are difficult to reach through  
26 education and labeling changes alone, which would  
27 include the limited English-speaking as well as  
28 visually impaired, just to comment on two groups.



1                   And as we think through the strategies,  
2           there being an educational component to any way  
3           forward, that we should take that into account  
4           with regard to testing and assuring that methods  
5           are thought through for how to reach these  
6           difficult populations in terms of educational  
7           programs, and educational programs alone may not  
8           be effective in this regard.

9                   DR. NELSON: Thank you.

10                  Ms. Landis.

11                  DR. LANDIS: Thank you. Winnie Landis.  
12           I just wanted to paint a picture, as a pharmacist.  
13           When you deal with patients every day that have  
14           needs for products that are out front, because  
15           they really have a need, plus what comes through  
16           on prescription, every day I fill prescriptions  
17           from physicians where there is a dose between 6  
18           and 8 grams of acetaminophen, and every day I'm  
19           trying to correct and be that middle-man between  
20           the physician and the patient.

21                  We've talked so much about education for  
22           the patient, but not so much about education for  
23           the physicians and the pharmacists and the  
24           caregivers in the process.

25                  It starts at the beginning. I feel like  
26           this is a little bit like Swiss cheese. We're  
27           trying to fix it at the very, very end, rather  
28           than looking at what's caused at the beginning of

1       it. I think everybody has to step up on this. I  
2       think physicians need to be more knowledgeable.

3               I think there can be some very simple  
4       things that can happen at the pharmacists' level  
5       and hold them accountable, whether it's putting a  
6       limit of six doses per day on a prescription  
7       label -- that will go much further than trying to  
8       spell out acetaminophen, which patients don't  
9       understand.

10              In my world, acetaminophen translates to  
11       a Tylenol or a non-aspirin product. The word is  
12       very difficult for them to understand. So I think  
13       you have to keep it simple. I think we need to  
14       educate those at the top of the ladder, and maybe  
15       us looking at those products that are on  
16       prescription that have doses that are attached to  
17       it of more than 500 milligrams of acetaminophen --  
18       and I know that there was some discussion earlier  
19       outside of this as far as the propoxyphene doses.  
20       That's probably one of the most common ones I see  
21       an overdose in as far as coming from a physician:  
22       The one, two, three, four -- one or two every  
23       three to four, or the one, two, four six -- one or  
24       two every four to six.

25              And even though I try to intervene with  
26       the physician or with the patient, if it's on the  
27       label, which we're supposed to put in from the  
28       physician, the patient will side with, but that's

1        what my doctor wants me to take.

2                So I would ask this committee to look at  
3        the whole process that we have here before us, and  
4        let's find ways that we can all work together --  
5        hold me, as a pharmacist, accountable for what  
6        goes to the patient, but also help me on the side  
7        with the physician.

8                Also with that, it's not just one  
9        physician. We're in a very broken system where  
10       patients see multiple physicians and they shop at  
11       multiple places, and yet we're trying to fix a  
12       system where we don't have all that information.

13               We have patients that may be going to a  
14       Wal-Mart and mail order and a CVS and a drug store  
15       or a grocery store, and I can capture some of that  
16       information, probably more so than what the  
17       physicians know on their side, because I at least  
18       have a database of some of the information, and I  
19       can look at see what they have, and try to  
20       intervene if they're asking for information on an  
21       OTC product, but it's not complete.

22               And I would encourage the FDA to look at  
23       what we can do to better utilize that. I know  
24       it's outside of their jurisdiction, but a  
25       behind-the-counter, pharmacist-only category would  
26       certainly help in a position like this where we  
27       have a product that has concerns and yet is needed  
28       by the public.

1                   So I would encourage that we look at  
2 other alternatives that we have here, and yet  
3 let's not put the burden on the patient; let's  
4 look at ourselves first.

5                   DR. NELSON: We've reached my artificial  
6 time limit, but we can probably go on a little bit  
7 more, because I think we'll have some room.

8                   But what I'd like to do -- I know this is  
9 going to be difficult -- is to really ask  
10 everybody to limit your comment to maybe one  
11 minute and just bring out your most important  
12 points straight away. This way we'll get as many  
13 people to speak as possible. I'd appreciate if we  
14 could try to do that. The list just keeps  
15 growing. Okay.

16                  Dr. Walker-Harding.

17                  DR. WALKER-HARDING: Thank you. I had --  
18 you know, sitting here, still, I'm very struck by  
19 the fact that the majority of the people that seem  
20 to present with overdoses are between the 12 and  
21 24-year age group, and yet none of our things that  
22 we're going to vote on specifically are looking at  
23 that group.

24                  I also -- I don't think it's a  
25 coincidence it's that group, because that's also  
26 the same group that has the least access to  
27 healthcare. It's the group that has the least  
28 healthcare utilization. So these are people who

1 may not even present to the doctor. These are  
2 people who are in mental health pain and physical  
3 pain, and they're going to go get what they can  
4 access the easiest and the cheapest to get rid of  
5 that pain in whatever way they're doing it.

6 And it's also the people -- again,  
7 looking at education does not change behavior --  
8 this is a group of people who do not have a skill  
9 set yet to help augment any knowledge that they  
10 gain.

11 So I'm very concerned that we don't just  
12 end up with an education recommendation because,  
13 with this age group, the one that is actually  
14 presenting with the highest percentage of  
15 overdoses, education alone and even relying on  
16 them accessing some kind of healthcare is not  
17 going to be enough.

18 DR. NELSON: Thank you.

19 Dr. Omogui.

20 DR. OMOGUI: Yes. I want to comment on  
21 the combination opioid/acetaminophen. I believe  
22 this is a low-hanging fruit and where actually can  
23 quickly be taken in a way that is not -- in a way  
24 that is cost-effective and not disruptive.

25 We have combination opioids of  
26 hydrocodone/acetaminophen that have 750 milligrams  
27 of acetaminophen in each tablet, with patients --  
28 a patient taking ten tablets of that goes straight

1 to 7.5 grams a day. And these are patients who  
2 are taking these medications chronically for  
3 months or for years. And I have not seen any data  
4 that justifies that kind of amount of  
5 acetaminophen in each tablet.

6 I believe that -- and unfortunately this  
7 is not one of the options, but I believe that by  
8 reducing the amount of acetaminophen not to exceed  
9 325 milligrams in each tablet will enable the FDA  
10 to keep the schedule III of hydrocodone, at the  
11 same time minimizing the risk of overdose.

12 This will clearly be engineering safety  
13 because when pharmacies, like the speaker a couple  
14 of minutes talked about seeing patients come in  
15 there with ten tablets, 8 grams of acetaminophen,  
16 having -- this can be very quickly addressed  
17 without disrupting the schedule or taking those  
18 off the market.

19 I think we see this only with the  
20 hydrocodone. I don't see 750 milligrams  
21 acetaminophen with oxycodone products. Most of  
22 these patients, when they're titrating up on these  
23 combination drugs, are completely disregarding the  
24 acetaminophen. They are titrating up for their  
25 pain based on the opioid, the hydrocodone.

26 So I think this should be one of the  
27 options that should be considered and that we  
28 should get these high-dose acetaminophen tablets

1 off the market, the combination of hydrocodone  
2 with 750 or with 500. Thanks.

3 DR. NELSON: Thank you.

4 As we go around, I would just ask again,  
5 if the topic you're going to discuss is really  
6 directly pertinent to one of the options, you  
7 might just save it for that, because it might  
8 carry a little bit more impact at that point. And  
9 if we could focus on the more global issues, or  
10 the more public health-focused issues --  
11 Dr. Chojkier.

12 DR. CHOJKIER: Thank you. First I want  
13 to expand on the comments of Dr. Levine. I am  
14 also a hepaologist, and we have a clear greater  
15 susceptibility among females than males for  
16 alcohol use and abuse. And so this should be  
17 corrected. Indeed, the current -- the National  
18 Institutes of Health in clinical trials accepts  
19 two drinks -- whatever that equivalent is for  
20 females, while three are accepted as a threshold  
21 for males. So this is something that we will have  
22 to consider as a global strategy.

23 The second issue the we haven't  
24 addressed, at least not clearly, is we have  
25 millions of people in the United States with liver  
26 diseases, and there is not a precise working group  
27 that have recommended any particular dosage for  
28 that group of people.

1           The most frequent utilization is that, in  
2           many liver centers, we use 2 grams, but this is an  
3           arbitrary number. But the vast majority of  
4           physicians have no knowledge of what should be the  
5           dosage for that population.

6           So there are a number of issues I think  
7           that we can improve dramatically upon, and make an  
8           impact on safety in a very rapid way. That's all.

9           DR. NELSON: Thank you.

10          Ms. Day.

11          MS. DAY: As we consider dosage reduction  
12          and considerations of efficacy, I would just like  
13          to express disappointment with the data that we've  
14          been presented about efficacy. It's good as far  
15          as it goes. We compare efficacy for different  
16          doses, and sometimes different entities and so on.  
17          But there is a lot of evidence that other means  
18          can be used to treat moderate to mild pain through  
19          other means -- behavioral means. There are many  
20          pain clinics. There is a lot of NIH funding for  
21          other -- for behavioral treatment of pain that  
22          seems to work.

23          It's too late for us to go into all that  
24          now, and I know this is the Food and Drug  
25          Administration, not the Food and Behavior  
26          Administration, but as we look at efficacy of  
27          various products, it would be nice to be able to  
28          compare them -- compare the efficacy of these



1 products to other means. And there's a tremendous  
2 of research out there.

3 So right now, as we make all these  
4 considerations, we're missing part of the data,  
5 and I urge the FDA to bring in these types of  
6 studies in future meetings where pain is being  
7 addressed.

8 DR. NELSON: Thank you.

9 Dr. Pollock.

10 DR. POLLOCK: I have a procedural  
11 question for Dr. Johnson, I think. There's a  
12 couple of things that we've talked about and that  
13 were included in the briefing material that we're  
14 actually not going to be asked to vote on today,  
15 particularly the dosing guidelines for pediatric  
16 patients under two, and the single pediatric  
17 formulations.

18 Are those appropriate things to include  
19 under option 11? Or what's going to happen with  
20 those topics?

21 DR. JOHNSON: Specific to the dosing  
22 under two, we have ongoing activity related to  
23 that as I think Dr. Ganley suggested yesterday --  
24 the best way to solve this problem of  
25 acetaminophen overall was to decouple all of the  
26 various problems, and be able to move forward on  
27 segments.

28 So the under two problem will be

1 addressed, and we will need pediatric experts in  
2 particular, in addition to this general  
3 committee, to look at that problem.

4 And the options that we don't  
5 specifically vote on here -- and I think the  
6 comment earlier was that there's no particular  
7 question about lowering the dose of acetaminophen  
8 in Rx combos. We took those out, thinking that  
9 OTC would take the lead, and we would use your  
10 advice on the OTC product dose lowering to look at  
11 the Rx. But we hear your concerns about the Rx  
12 dose.

13 DR. POLLOCK: Thanks.

14 DR. NELSON: Dr. Krenzelok.

15 DR. KRENZELOK: Thank you very much. I  
16 have a little different perspective than a lot of  
17 people around the table -- not everybody, but a  
18 lot. I'm a clinical toxicologist. I'm director  
19 of the Pittsburgh Poison Center. And last year we  
20 handled about 55,000 exposures; about 3,000 of  
21 those were acetaminophen. So we see this on a  
22 daily basis.

23 And I think we've heard a lot of numbers  
24 here. We've heard numbers bantered around from  
25 the national poison data system. I took the  
26 liberty of adding up the numbers and, for the last  
27 ten years, there are about 1.2 million exposures  
28 reported to American poison centers over the last

1       ten years involving acetaminophen by itself or in  
2       combination.

3               But, remember, those are exposures.  
4       Those aren't necessarily poisonings. And we look  
5       at the magnitude of 25 billion doses of  
6       acetaminophen, 100 million people taking  
7       acetaminophen each year -- those numbers are  
8       relatively in line with other products and other  
9       exposures we have.

10              The other comment I wanted to make deals  
11       with pediatric exposures. Pediatric exposures  
12       account for more exposures than any other group --  
13       and I'm talking about children less than six years  
14       of age. I don't want to minimize that in any way,  
15       but there have only been ten deaths in the last  
16       eight years that I'm aware of involving kids less  
17       than six years of age and involving acetaminophen.

18              And the typical acetaminophen exposure  
19       that we deal with involving a small child is  
20       really treated -- again, not to minimize it, but  
21       it's sort of glass of milk for the child and a  
22       tincture of reassurance for the parent.

23              So you've heard a lot of numbers, you've  
24       heard a lot of things that make it sound like this  
25       horrible, egregious substance, but it really isn't  
26       that bad, and most of the exposures we have really  
27       have very, very favorable outcomes. Thank you.

28              DR. NELSON: Thank you.

1 Dr. Lorenz.

2 DR. LORENZ: Yes. On one hand I'd like  
3 to reiterate the opinion expressed by several of  
4 our panelists that I think the most important  
5 target for our action is unintentional harm, both  
6 in adults and children, and that I very much share  
7 the thinking that education is a weak intervention  
8 and that we are really looking for more concrete  
9 steps and opportunities to impact that  
10 unintentional harm.

11 Really, globally to the FDA, one of my  
12 concerns is that it would have been very  
13 helpful -- and this is a suggestion for the  
14 future -- to have an explicit modeling of the  
15 placebo options that we're being presented with.  
16 In particular, it would be helpful to understand  
17 both the key assumptions that drive those policy  
18 options and, in terms of modeling, understanding  
19 how the variables might inform those models so  
20 that we could focus on a sensitivity analysis,  
21 effectively, in understanding the risk and benefit  
22 of these various alternatives.

23 Because I'm sure that we all share, at  
24 the end of the day, the conclusion that there is  
25 nothing without risk and nothing without potential  
26 benefit in terms of what we've been offered here.

27 So that is something I think that would  
28 help us deliberate more effectively in the future.

1           But in terms of specific options, one of  
2 my observations is that with regard to combination  
3 products, one reason they seem to be so popular is  
4 because they fill an important need. And so one  
5 of my cautions, as a clinician, is that the  
6 barriers to eliminating combination products  
7 entirely may relate to patient need; they also  
8 relate to provider discomfort and inability to  
9 address pain through stronger opioids.

10           And so there may be important options to  
11 take in the regulation of the combination  
12 marketplace, including limiting unit doses of  
13 acetaminophen in such products. But we do have to  
14 remember that they are prescribed often in the  
15 context of chronic pain, an answer -- or a problem  
16 that we don't often have effective answers or  
17 systems for delivering care to ameliorate.

18 Thanks.

19           DR. NELSON: I guess I'll make my comment  
20 at this point as well, having been on the list a  
21 few times and crossed my name off.

22           But, you know, risk assessment to me is  
23 probably the most important thing that we really  
24 have to get our hands around, and I don't know the  
25 way to do it, and I've asked FDA in the past  
26 multiple times, and they don't really have an  
27 answer.

28           One of the public speakers yesterday

1 brought up the issue that a drug was pulled from  
2 the market after there were three deaths, yet, you  
3 know, there are several hundred deaths a year for  
4 acetaminophen and it's still on the market.

5 Maybe if the drug was coming up for  
6 initial approval, it might undergo a different  
7 course of events and perhaps have a risk  
8 mitigation plan attached to it once it was  
9 marketed.

10 On retrospect, or working backwards, it's  
11 obviously much harder to do that, which is perhaps  
12 why we're here today trying to put these types of  
13 ideas into place in order to get a better handle  
14 on it.

15 An analogy that came up yesterday that I  
16 thought was actually fairly good -- and it's not  
17 mine, but I'll quote it anyway -- was the airplane  
18 analogy, which I thought was quite good. You  
19 know, there are millions and millions of people  
20 flying on an airplane every day, but every time an  
21 airplane crashes, there's a full-blown  
22 investigation into the root cause and what  
23 happened with it.

24 And just like there are millions and  
25 millions of doses of acetaminophen taken every  
26 day, this is our root cause into what the problem  
27 is -- and I think we really have to get a sense as  
28 to what the underlying cause is in order to really

1 fix the problem.

2 Now, one of the problems we're facing  
3 today is that there's a boatload of different  
4 issues we're struggling with, which dilutes each  
5 of them, but it's important that we cover each  
6 one.

7 And I'll let you comment in one second --  
8 and perhaps you'll be able to give me an answer --  
9 I'm sure you can't -- but the idea that we have to  
10 really balance risk plus -- or risk and benefit is  
11 what makes this just so difficult to do.

12 Dr. Kweder.

13 DR. KWEDER: The answer is yes to your  
14 question, but I really did want to comment on the  
15 last speaker who suggested that FDA try to, you  
16 know, present some policy option models. And to  
17 tell you the truth, we have tried to do that, and  
18 none of the option models that we could present we  
19 felt we could really stand behind and would pass  
20 muster.

21 And the reason for that is that this is  
22 not a problem that has developed overnight, and it  
23 doesn't have firm constraints around it. There  
24 are -- as you've heard from the speakers  
25 presenting over the past few days, there are so  
26 many factors that we cannot measure because of the  
27 way the product is used.

28 This would be a lot easier if this were,

1       you know, one product -- we were only talking  
2       about one product, and it was prescription. This  
3       is a product that has been evolving in use,  
4       growing in use, expanding in use, with multiple  
5       behavioral factors and environmental factors  
6       playing into what we see before us. So it is not  
7       something that has occurred very quickly.

8               Someone yesterday mentioned the case of  
9       what was affected to decrease the use of aspirin  
10      with Reye's syndrome. Well, we have studied that  
11      model, and that was a simple message. Awareness  
12      of it came about at a very sharp point in time.  
13      So the intervention could be very quick, and by  
14      bringing together multiple parties at the same  
15      time, it could be addressed, and it was a  
16      remarkably successful public education campaign.  
17      Remarkably successful.

18             You know, we've looked at that -- we've  
19      studied that intensively to try to understand the  
20      parallels, and in fact, there are precious few.

21             And also with regard to modeling, I think  
22      one of the best examples of an attempt to model  
23      was presented yesterday in the morning, and I  
24      think there were an awful lot of questions -- we  
25      had them as well -- about what were the  
26      assumptions going into those models, and we could  
27      only assume the assumptions; most of them were not  
28      stated, and many of us wouldn't have agreed with



1           them.

2                       So we thought about doing that and  
3       decided it would probably be best to capitalize on  
4       your own clinical and other experiential  
5       expertise, and it's why there is such a wide range  
6       of perspectives and experiences sitting around  
7       this table.

8                       So please know that it's not for lack of  
9       trying.

10                      DR. NELSON: I didn't think it was.  
11       Thank you.

12                      There are three more people at the table,  
13       so it should be three more minutes, I think, until  
14       we get to vote -- four, okay. But that's going to  
15       be it. Okay?

16                      Dr. Kerns.

17                      DR. KERNS: Yes. I really don't think I  
18       can say it any better than my colleague,  
19       Dr. Lorenz, but I really do find myself at a  
20       disadvantage, feeling disappointed overall that  
21       this issue about acetaminophen is taken out of  
22       important context, context of other  
23       over-the-counter and prescribed analgesic  
24       medications, and the broader context of pain  
25       management and efficacy or effectiveness. I'm  
26       very concerned about the implications of --  
27       downstream implications of any rulings or changes  
28       in current regulatory climate as an outcome of

1       this meeting because I really think that the data  
2       have not been so compelling -- I guess I agree  
3       with my colleague across the table about the  
4       degree of risk related to acetaminophen and acute  
5       liver failure, specifically in the context of  
6       unintentional harm.

7               The only context that I think is  
8       important is the -- lot of data about suicide or  
9       intentional harm. Without putting those data in  
10      the context of suicide, an enormous public health  
11      crisis in this country, I think it's very hard to  
12      assimilate or make specific judgments based on the  
13      isolated information about acute liver failure.

14             DR. NELSON: Thank you.

15             Dr. Wolfe.

16             DR. WOLFE: Just to briefly add a decade  
17      to what Dr. Kramer was saying. It's actually at a  
18      meeting here in 1977 there was a conclusion, do  
19      not exceed recommended dose because severe liver  
20      damage may occur.

21             That forceful message didn't get  
22      incorporated until a few months ago. So it's  
23      taken a very long time.

24             But looking forward, I am an optimist,  
25      mainly, and I believe that when we look back ten  
26      years from now, to now, there will, in fact, be a  
27      reduction in the amount of acetaminophen liver  
28      toxicity. And I think that it will not be due to

1 any one factor.

2 The U.K. started to work on this series  
3 with the pack reduction. I think that we need to  
4 look at each of these options and say, we're never  
5 going to be able to say that one of them was the  
6 sole effect, the combination of regulatory options  
7 itself informs the public.

8 So I think that as we go through this  
9 list, we will, as best as possible, look at the  
10 benefit and risk, the possible downside of any of  
11 these options, and add as many as we possible can,  
12 because that's the only way that harm reduction,  
13 after all this period of time during which we  
14 actually increased the dose after we knew it would  
15 cause liver toxicity, will occur.

16 I look forward to this discussion. I  
17 yield my ten seconds to someone else.

18 DR. NELSON: Dr. Todd.

19 DR. TODD: Thanks. Knox Todd, and I'll  
20 take less than a minute. I'm just going to make a  
21 brief observation that I'm sure all of you have  
22 thought about, and that is the demographic shifts  
23 and implications.

24 Policy takes a long time to implement.  
25 Reversing policy takes much longer to achieve.  
26 And I share Dr. Kerns' concern that some of this  
27 data is very iffy, and I worry about making the  
28 wrong decision here.

1 I do know that the more susceptible  
2 population to acetaminophen injury is a younger  
3 population, in general, certainly for intentional  
4 injury. And the population that is at great risk  
5 from switching effect, particularly  
6 non-steroidals, are the older population. And  
7 that's exactly what we will see, and that's one of  
8 the key and, I think, firm data points one can  
9 take out of this.

10 So those -- thinking back to Ken  
11 Rothman's risk analysis yesterday, I know that I  
12 see, in the emergency department, much more  
13 non-steroidal-induced hypertension, congestive  
14 heart failure, renal failure, GI bleed -- and I  
15 see that every day, so I'd just be cautious about  
16 the susceptible population, demographic shifts,  
17 policy changes that take a long time to reverse if  
18 we're wrong.

19 DR. NELSON: Thank you.

20 Dr. Covington.

21 DR. COVINGTON: Thank you. I'd just like  
22 to express a concern that I think we may be  
23 minimizing a little bit the issue of hydrocodone  
24 and its combination with acetaminophen. We saw  
25 DAWN data that, per prescription, there aren't a  
26 lot of people coming to the emergency room with  
27 problems from hydrocodone/acetaminophen, but  
28 numerically, it's an order of magnitude worse than

1 anything else that comes to the emergency room,  
2 with the exception of oxycodone.

3 In a sense it seems to me that -- I don't  
4 know of anything special about hydrocodone. It's  
5 substantially more potent, orally, than morphine  
6 is, so basically we have limited its abuse, as was  
7 said yesterday, by combining it with a poison so  
8 that you can't abuse it as easily as you can abuse  
9 OxyContin.

10 And the whole idea of protecting the  
11 public by mixing a poison with your medicine I  
12 find troubling, and in essence that's what we've  
13 done.

14 I think the popularity of this drug  
15 largely relates to the fact that it's extremely  
16 convenient to prescribe. You can do it by phone.  
17 In Ohio, advanced practice nurses can prescribe  
18 it. So there are of lots of reasons that account  
19 for the popularity of this drug that have nothing  
20 to do with the fact that acetaminophen may have  
21 some opioid-sparing effect.

22 And I think that if we don't take the  
23 opioids out of -- I mean, if we don't take the  
24 acetaminophen out of the pill, it's critical that  
25 we reduce the concentration out of the pill  
26 because we know that patients in chronic use are  
27 going to escalate the dose, and when they do, they  
28 will reach toxic levels of acetaminophen.

1 DR. NELSON: Okay. Thank you.

2 I've done some recalculations on the  
3 time, and we're going to be fine. Before we  
4 actually move on to the options and questions, I'm  
5 just going to explain to you a little bit about  
6 the voting procedure itself.

7 We're going to be using this electronic  
8 voting system for the first nine questions, and  
9 it's been adapted to the special requirements for  
10 the questions prepared for this meeting.

11 Each of your microphones should have two  
12 stickers, one with your name on it -- and make  
13 sure that's correct -- and another with the  
14 labels -- another one that has the voting letters  
15 attached to it.

16 Just confirm your name sticker is correct  
17 and that the sticker labeling the buttons is still  
18 there and is marking the buttons to the far left  
19 of the console. So they are flashing, it looks  
20 like, now. It should say A, B and C. The three  
21 buttons starting to the left have been labeled.  
22 Okay.

23 Is there anybody that has a question  
24 about this at this point, or the labeling?  
25 Everybody is okay? Any issues? Good. Okay.

26 Before we start to vote, I'd like to make  
27 sure that all discussion of the question is  
28 complete, or as complete as it can be. Once we

1 being the vote, please press the button that  
2 corresponds to your vote. After everyone has  
3 voted, the voting will be completed.

4 We will -- I'm reading this; I'm not  
5 making this up.

6 We will display the results of the vote  
7 on the screen, first as a tally result, which I  
8 will read into the record, then votes of each  
9 individual will be displayed on a chart.

10 Because of the large numbers of  
11 participants, and the many questions we will have  
12 to answer, we will not be taking the time to have  
13 each member read the vote into the record, as we  
14 often do, but we will have an opportunity for  
15 anyone who wishes to clarify or explain their vote  
16 to do so. And we'll go more into that after we  
17 vote, and we'll see how that plays out.

18 So at this point, I'd like to move on to  
19 the first option, which actually has two questions  
20 associated with in it, and that would be from the  
21 options paper. It's option 1a. You've all  
22 probably looked at the general considerations  
23 already, but keep those in mind as we move  
24 forward.

25 And in addition to the general  
26 considerations, option 1 has some additional  
27 considerations. So option 1 is to reduce the  
28 current dosage strengths of acetaminophen in

1 nonprescription products. This could include the  
2 maximum adult daily dose, the maximum single adult  
3 dose or the maximum dosage strength.

4 So the discussion for now -- and I think  
5 it's probably okay to discuss both question 1 and  
6 question 2 simultaneously, but I think we're going  
7 to vote on them separately. Okay?

8 So question 1 for the vote is, Do you  
9 recommend that the maximum total daily dose of 4  
10 grams per day of acetaminophen in nonprescription  
11 single-ingredient and combination products be  
12 lowered?

13 And question 2, as we deliberate, Do you  
14 recommend that the maximum nonprescription single  
15 adult dose be limited to 650 milligrams?

16 Dr. Farber?

17 DR. FARBER: Neil Farber, UC San Diego.  
18 So in reference to the discussion a little bit  
19 before about the low number of fatalities that  
20 occur with acetaminophen overdosage, one must also  
21 consider the fact that there is another cost here  
22 in terms of morbidity, both ER visits and  
23 hospitalizations, and we saw data yesterday that  
24 it's about 40,000 total ER visits per year, with  
25 about half of them being unintentional, which  
26 amounts to about 20,000 ER visits per year. So  
27 it's not negligible.

28 In terms of -- I just want to make that



1 comment.

2 In terms of question 1, going from 4  
3 grams per day to a lesser number I don't think  
4 impacts greatly the manufacturers. There is no  
5 change in formulation, et cetera. It's simply a  
6 labeling in terms of what the recommended maximum  
7 dose is.

8 I don't know that it was have tremendous  
9 impact, but it's something that we can do. In  
10 terms of going to the lower individual doses, that  
11 obviously does have impact.

12 However, on the other hand, we have seen  
13 that there are no differences based on the  
14 Cochrane data that were presented. And one has to  
15 look at this as a risk/benefits ratio, the risk  
16 being -- in terms of the change, the risk being  
17 basically a financial one, for the most part, and  
18 perhaps somewhat less effectiveness, although  
19 there are no good data to support that -- and the  
20 fact that patients might entertain a higher risk  
21 if, in fact, they're having some higher pain and  
22 have to take three pills instead of two.

23 So that's what I think we need to weigh  
24 when we're looking at this.

25 DR. NELSON: Thank you.

26 Dr. Kerns.

27 DR. KERNS: Yes. I appreciate the  
28 comments and the findings of the Cochrane

1 interview. My own understanding of the data that  
2 were presented yesterday was, one, that there  
3 really are not compelling data to support the idea  
4 that there's a greater risk -- that there is  
5 specific risk associated with 4 grams per day, and  
6 two, it seemed to me that the only two studies  
7 that were presented that had the power -- that  
8 were specifically powered to directly compare a  
9 dose of 1,000 milligrams versus a lower dose found  
10 support for increased efficacy of the higher dose.

11 And, for me, the idea that there may be a  
12 cost in terms of availability of less efficacy is  
13 not one to be minimized, given the problem of  
14 chronic pain in this country as a public health  
15 crisis that cannot be minimized.

16 And the inability to understand the  
17 potential impact of this kind of change, either  
18 question 1 or 2, on the use of other medications  
19 and pain care more generally I think is -- without  
20 those data, it's really hard to support either of  
21 these recommendations.

22 DR. NELSON: Dr. Olsen.

23 DR. OLSEN: I want to speak as I think  
24 the only rheumatologist here, so in terms of  
25 patients with arthritis, that we have talked a lot  
26 about risk and very little about efficacy as has  
27 been brought up by some of the other speakers. In  
28 terms of patients with arthritis -- we're talking

1 about chronic long-term use -- the data we have  
2 seen about efficacy in the last couple of days  
3 really are short-term dental pain models which I  
4 don't think speak to the issue of what happens on  
5 a chronic basis.

6 So we don't have a lot of data on which  
7 to make this decision that we're going to have to  
8 make anyway as to whether, as you approach that  
9 maximum dose of 4 grams per day, you probably do  
10 increase your risk. What's less clear is whether  
11 you actually increase benefit proportionally.

12 My personal opinion, from just observing  
13 the use of this medication in arthritis, is that  
14 it's unlikely that you increase much efficacy as  
15 you approach that 4-gram limit, while you are  
16 probably increasing the risk, so that the  
17 risk/benefit ratio may actually deteriorate. But  
18 that's based on observation, and I'm just pointing  
19 out we have limited data.

20 DR. NELSON: Dr. Engle.

21 DR. ENGLE: I wanted to address this from  
22 the pharmacist's point of view and from somebody  
23 who has dealt with nonprescription drugs in the  
24 community setting for a large number of years.

25 My concern about changing the labeling to  
26 going to less than 4 grams a day, or changing the  
27 doses, is that consumers know what they've taken  
28 in the past. It's a learned behavior. Doctors

1 know what they've prescribed or told patients they  
2 can take in the past. And they're going to do it  
3 anyway. I mean, we had tons of data that says  
4 nobody reads the label -- not nobody, but a small  
5 [sic] percentage of patients don't read the label  
6 anyway.

7           So my concern is we take it off the  
8 label, we changed our recommendations; yet  
9 prescribers and patients know they can take this,  
10 so there's less trust in the label. So what  
11 happens is they think that, okay, it's not on the  
12 label, but I know I can do it -- and it sort of  
13 discounts the rest of the warnings that are on  
14 there.

15           So consumers then kind of pooh-pooh  
16 what's on that label anyway. And it happens with  
17 the non-steroidals because they all know that  
18 prescription doses are higher and that you can  
19 take it. So it's something that needs to be  
20 considered.

21           Same thing with the osteoarthritis  
22 recommendations. They are 4 grams a day. So a  
23 doc may say to the patient, go ahead and take it,  
24 but then they don't have the information on the  
25 label to substantiate that.

26           To me, it's similar to this peds dosing  
27 information. We say that we need that for kids  
28 under the age of two, and that's important. Yet

1 we're saying we may take this information off the  
2 label, knowing that some patients may be taking  
3 the 4 grams a day, or they're going to end up  
4 taking the three 325-milligram tablets to get  
5 closer to taking two 500s.

6 So I just wanted to bring that  
7 perspective. In the OTC environment, there are  
8 learned behaviors. There are patients that know  
9 this information, and they're going to do it  
10 anyway, and now we're taking information off the  
11 label that might help them do it in a safer way.

12 DR. NELSON: Dr. Benowitz.

13 DR. BENOWITZ: When I came here, after  
14 reading the documents, I thought that reducing the  
15 maximum dose would be a good idea, but having  
16 heard various discussions, one, it's not clear to  
17 me that there is very much evidence at all that 4  
18 grams a day is toxic, and 3200 milligrams would be  
19 less toxic. There is very little evidence that  
20 we've seen at all about the fact that 4 grams a  
21 day is substantially toxic.

22 I think Dr. Olsen's point is an important  
23 one, and what I was looking for was some evidence  
24 comparing 4 grams a day versus 3200 milligrams a  
25 day, which are the two limits we're talking about,  
26 to see if it makes a difference for chronic  
27 arthritis, because that is really a critical  
28 issue. And we don't have those data.

1                   So the only thing that really is  
2           compelling about reducing the dose would be for  
3           people who are using it incorrectly: Would you be  
4           less likely to have a problem if you're using it  
5           incorrectly and you use a 500 instead of a 325?  
6           So if you're using it with other products, it  
7           would be a higher risk.

8                   And so that, to me, is the only advantage  
9           I could see to reducing the maximum dose or the  
10          dose per tablet.

11                   DR. NELSON: Thank you.

12                   Dr. Gellad.

13                   DR. GELLAD: I wanted to bring up the  
14          issue, which I -- intuitively is a problem to me  
15          is whenever I prescribe opioid combinations to  
16          patients, it's very easy to tell them, do not take  
17          more than 4 grams of Tylenol a day, or 4,000  
18          milligrams. And I'm not sure how I'm going to  
19          explain to them, do not take more than 3,250  
20          milligrams, or -- you know, realistically, when  
21          I'm talking to the patient, it's going to be much  
22          more difficult for those kind of limits.

23                   In general, my feeling is that, as the  
24          rheumatologist colleague said, that the added  
25          benefit may not be worth the potential added risk  
26          of 4 grams versus lower dosages. But -- that  
27          would be my comment.

28                   The other thing is I'm not sure why it

1 has to be 4,000 versus 3250. It can be 3500, you  
2 know, if you limit it to seven pills rather than  
3 eight pills. But I agree that we don't have -- we  
4 did not see any data directly comparing these two  
5 different doses per day, which would be useful.

6 DR. NELSON: Dr. DeNisco.

7 DR. DeNISCO: Richard DeNisco. As I go  
8 back through the information provided us, it  
9 almost seemed like there was a dose creep from  
10 when these things were approved, and then the  
11 doses went from 325, 500, now even 750 milligrams  
12 in some combination products -- and I think that  
13 was not the indication or the intention of the  
14 original over-the-counter approval. I don't  
15 know -- I certainly wasn't there; I don't know.

16 But if I consider -- the other thing I  
17 just wanted to briefly say was that we still are  
18 in a situation where we can prescribe a higher  
19 dosage, or a dosage closer to 4 grams, and make  
20 that a prescription dose. It's sort of analogous  
21 to having a lower, less risky non-steroidal dose  
22 and a higher, possibly riskier dose of  
23 non-steroidals being a prescription strength and a  
24 over-the-counter strength -- and it seems like the  
25 greater milligrams just allows a larger, you know,  
26 more effective stronger label marketing tool, and  
27 I don't know why the dosage has been actually  
28 allowed to creep up on the over-the-counter

1 medications.

2 DR. NELSON: Thank you.

3 Dr. Kramer.

4 DR. KRAMER: Judith Kramer. I'd like to  
5 make two comments on this question. One is that  
6 it seems to me that both parts of this question  
7 are directly targeted to reducing unintentional  
8 overdose, which is something that several people  
9 on the panel said was a major goal.

10 It's not so much that, you know, 3250 or  
11 4,000 is the issue. But if you reduce total  
12 amount per tablet, or the maximum single dose,  
13 then if people are taking multiple preparations,  
14 it's just less likely to exceed the target. So  
15 I'd like to make that comment.

16 But the other comment is that it's  
17 bothering me that, as you look at the series of  
18 questions we're addressing, this is focused on the  
19 maximum single nonprescription dose, question 2.  
20 And we heard the manufacturer say that they're  
21 going to be recommending that the dose of  
22 acetaminophen be one 500-milligram tablet.

23 So it's kind of interesting because we're  
24 now recommending, for an arthritis patient, that  
25 you take 500, not 1,000, and the alternative, if  
26 you had 325 milligrams per tablets, the  
27 recommendation could be 650 for a single dose, so  
28 that you'd have probably more likelihood that, if



1       there is any slight difference in efficacy, you  
2       know, maybe 650 is better as the single dose.

3               So it bothers me that we're only  
4       addressing the maximum and not thinking about what  
5       the landscape will look like when we recommend now  
6       500 milligrams as the dose people should take.

7               So just in consideration of that as well.

8               DR. NELSON: Thank you.

9               Dr. Raja.

10              DR. RAJA: In trying to decide, you know,  
11       where we can make an impact, whether it should be  
12       changes in the over-the-counter drug dosage or  
13       whether it should be in prescription drug, I was  
14       kind of torn by the fact that the epidemiological  
15       data that was provided was considerably different.

16              In the morning we heard yesterday from  
17       Laura Governale that 80 percent of the entire  
18       market was from OTC products and only 20 percent  
19       from prescription drugs. But, again, when we  
20       heard from industry, from Dr. Suydam, it was a  
21       50/50 of the two drugs.

22              So the question in trying to decide where  
23       should be the changes -- should it be more related  
24       to OTC or should be it be secondary to  
25       prescription drugs -- we don't seem to have good  
26       epidemiological data that is consistent to say,  
27       where is the source of the estimate coming from.

28              DR. NELSON: Thank you.

1 Dr. Todd.

2 DR. TODD: Thanks. Knox Todd. Just a  
3 quick point. The question -- in my emergency  
4 department what we do is we only stock 325s  
5 because it's cheaper for us, and we use of three  
6 of them. It's very simple. We're simple people  
7 in the ER. I think there is a potential risk here  
8 that just should be mentioned, and that is that  
9 the public begins to interpret this as a  
10 titratable agent as opposed to a ceiling dose  
11 agent, and indeed patients begin -- if two is  
12 good, three is better, four might be better -- and  
13 the potential is there to increase toxicity,  
14 particularly with regard to unintentional injury.

15 DR. NELSON: Thank you.

16 Dr. Covington.

17 DR. COVINGTON: Yesterday. I really have  
18 a question. The only comparative data that we had  
19 was, you know, the acute dental pain model, and  
20 the only chronic data that we had was the  
21 osteoarthritis model. And there were various  
22 dosage forms used in the osteoarthritis studies,  
23 and I'm wondering if anybody has done NNT  
24 calculations on those -- we really don't have  
25 good -- any data that I've heard so far that kind  
26 of compares the efficacy in the osteoarthritis  
27 model of the 1,000 versus 650-milligram dose.

28 I wondered if the FDA had done NNT

1           calculations on that data. No?

2                   DR. NELSON: An answer from that corner  
3 of the table?

4                   DR. CHANG: No, we didn't perform any NNT  
5 calculations on that data.

6                   DR. NELSON: Thank you.

7                   Dr. Griffin.

8                   DR. GRIFFIN: I want to first thank FDA  
9 for putting together the information packages. I  
10 found it very helpful.

11                   Secondly, I think that the -- there is  
12 not compelling evidence that 4 grams is toxic, but  
13 the toxic-to-therapeutic ratio is very close for  
14 an OTC drug.

15                   So I feel that the evidence for lowering  
16 the dose so that people don't unintentionally take  
17 more is compelling still.

18                   And I think, for chronic pain, I would  
19 like the option of having prescription available  
20 that people who are taking this chronically for  
21 arthritis maybe should be under the care of a  
22 physician or a healthcare provider, not taking  
23 this 4 grams a day on their own.

24                   DR. NELSON: Dr. Vaida.

25                   DR. VAIDA: Regarding question number 2,  
26 I think the thing that I'm struggling with is  
27 there is a 650-milligram tablet on the market, and  
28 unfortunately we just actually had two seasoned

1 healthcare professionals in our office take that  
2 combination four times a day, and -- taking two of  
3 them four times a day after a volleyball  
4 tournament.

5 So are we saying from 1,000 milligrams  
6 down to 650, or are we saying from 1300  
7 milligrams, or 1200 milligrams, 1300 milligrams  
8 down to 650? I'm just struggling with question 2  
9 because -- not to jump ahead; it seems like it  
10 plays into question 3, and we don't want to go  
11 backwards on that.

12 So I don't know if -- from a  
13 clarification standpoint, do we have any  
14 opportunity to say that the 500 milligrams, okay,  
15 and a 1,000-milligram dose -- if you are following  
16 what I'm saying.

17 DR. NELSON: It's not important that I  
18 follow it. It's important that the FDA follows  
19 it.

20 So do you have an answer or do you  
21 want --

22 DR. KWEDER: I think that you can caveat  
23 your responses as you choose. When we began this  
24 meeting, I will say we had not -- the  
25 discussion -- the proposal presented yesterday by  
26 McNeil of a single tablet 500 milligrams, or one  
27 of these higher doses, single-tablet dosing was  
28 not something that we had really considered

1 heavily because of the pattern of taking two that  
2 we're well aware of.

3 DR. NELSON: I have actually a related  
4 issue, which -- it does come up occasionally when  
5 you speak to people, which is that acetaminophen  
6 is usually consider to be a Q4-hour drug. And  
7 when you take 1,000 milligrams and you want to  
8 take it every four hours, that adds up to 6 grams  
9 a day pretty quickly, I mean, assuming you wake up  
10 in the middle of the night to take it -- and many  
11 people do.

12 So I don't know how to reconcile that  
13 issue either, because at some point, if you take  
14 1,000 milligrams four times, that leaves you with  
15 a substantial period of time that you're not going  
16 to be getting any pain relief, and that's perhaps  
17 where the extended-relief, 650-milligram, you  
18 know, dosage form came from.

19 DR. KWEDER: Right. And we would  
20 consider those extended-release things somewhat  
21 separately.

22 DR. NELSON: I know. I'm not -- I'm  
23 answering his question, I think. But my concern  
24 was the dosing. Q4 1,000 milligrams easily gets  
25 you above that.

26 I see Dr. Kuffner standing there  
27 patiently waiting to say something.

28 DR. KUFFNER: Sure. So -- I'm a

1 toxicologist by training, so what I wanted to do  
2 was actually go back and -- slide on, please --  
3 and actually look at, is there any incremental  
4 difference between the different formulations?

5 Because I think it's naive to think that  
6 one specific formulation with therapeutic use is  
7 leading to a greater rate of liver injury.

8 So within our database we have the  
9 advantage of being able to look at the  
10 325-milligram formulation, the 500-milligram  
11 formulation and the 650-milligram formulation.

12 So I went back and cut the data, looking  
13 at specifically when patients were using the  
14 formulation with therapeutic intent. And I think  
15 this really goes to the question of unintentional  
16 overdose.

17 And when you go back -- and these are the  
18 overdose cases. You look at it and you calculate  
19 a reporting rate. The number of cases that we  
20 have within our database, based upon the number of  
21 tablets distributed -- and this is over a  
22 five-year period -- what you actually see is the  
23 reporting rate for the 325-milligram formulation,  
24 the 500 and the 650-milligram formulations are  
25 similar. This does not appear to be a  
26 formulation-related issue.

27 DR. NELSON: Thank you.

28 Dr. Wolfe.

1 DR. WOLFE: In the FDA's AERS database  
2 there are a significant number of people in the  
3 unintentional category who had some form of  
4 hepatotoxicity under 4 grams. And we did, as  
5 mentioned a minute ago, slip up even when there  
6 was a lot of concern about liver damage, from 325  
7 to 500.

8 It would seem to me that when we're  
9 talking about -- all of this discussion right now  
10 is nonprescription where the ability of either a  
11 physician or a pharmacist to intervene is much  
12 less. I mean, a lot of acetaminophen and a lot of  
13 over-the-counter drugs are sold in places where  
14 there isn't any pharmacist.

15 So in terms of the balance between  
16 education and regulation, it seems to be most  
17 critical in the area where we're going to have  
18 essentially a patient and a shelf with a lot of  
19 brightly colored pills.

20 So I think that the coupling --  
21 question 1 and question 2 are obviously coupled,  
22 because the ability in the, again, nonprescription  
23 area to go down from 4,000 recommended maximum  
24 dose to 3200 is coupled to having the pill at --  
25 3250, coupled to having the pill available.

26 So I think that as something that has  
27 probably no downside significantly, the Dr. Fries  
28 presentation that was recommended -- or paper --

1 has been repudiated by Dr. Fries, the number of  
2 annual GI bleeding -- perforation, ulcer and  
3 bleeding deaths is way smaller, as he  
4 embarrassingly admitted at an advisory committee  
5 meeting.

6 So I think that for this group of people,  
7 nonprescription, there is evidence under 4,000  
8 grams for some liver damage, and that arguably  
9 this would have something that has a benefit more  
10 than it has a risk in terms of dropping the size  
11 of the pill and dropping the recommended dose.

12 There is, as other people mentioned,  
13 still the possibility for certain patients who are  
14 under the care of a physician to have, on a  
15 prescription basis, a higher dose. But I think in  
16 the over-the-counter setting, supermarkets,  
17 7-Eleven stores or whatever, we need to do more to  
18 protect patients.

19 DR. NELSON: Okay. Final comment,  
20 Dr. Kramer.

21 DR. KRAMER: Actually, I just needed  
22 clarification, maybe from Dr. Kweder, based on  
23 what Dr. Vaida said. I had interpreted question 2  
24 to suggest that an individual tablet would be 325  
25 milligrams, and the maximum dose would be 650.  
26 But now I'm thinking that I'm not clear what we're  
27 asked to vote on, because I wasn't aware of the  
28 650 individual -- is that immediate-release



1 tablet? So could you clarify whether this is  
2 assuming a 325-milligram unit dose in a tablet?

3 DR. GANLEY: Yeah. I think it would  
4 be -- this is Charlie Ganley. I think it would be  
5 a 325-milligram tablet. The 650-milligram tablet  
6 is an extended-release formulation, and the dosage  
7 is two tablets every eight hours -- I think that's  
8 it. So it's a total of 3900 milligrams per day.  
9 So that is an extended release.

10 I just want to clarify some questions  
11 that came up about what the dosing -- recommended  
12 dosing was for the proposed rule for the  
13 1,000-milligram dose, and that's not four to six  
14 hours; it's every six hours.

15 As you go down lower doses, the interval  
16 would be shortened to every three or every four  
17 hours, depending on what the dose is.

18 So a 1,000-milligram product should  
19 not -- that's recommending to tablets should not  
20 say every four to six hours. It should say every  
21 six hours, not to exceed 4 grams per day.

22 DR. NELSON: Okay. Thank you.

23 If there's no further discussion on this  
24 question, we will now begin the voting process.  
25 Please press the button on your microphone that  
26 corresponds to your vote. Remember the vote is A,  
27 yes, I recommend this change and consider it  
28 highly -- this is to question 1. B is, yes, I

1 recommend this change. And C is, no, I do not  
2 recommend this change. This is question 1.

3 So the results of the vote on question 1,  
4 yes, high priority, 11 votes; yes, 10 votes; and  
5 no, 16 votes.

6 I think what I'd like to do is -- I guess  
7 we should probably just ask if anybody has any  
8 pertinent pressing comments about why they voted  
9 no in particular, or yes, that they need to enter  
10 into the record for this moment.

11 Dr. Wolfe.

12 DR. WOLFE: I just want to suggest that  
13 those comments could be combined for 1 and 2,  
14 because I think that the logic is so closely  
15 related that, after we have done question 2, then  
16 maybe then people can explain --

17 DR. NELSON: That would be fine. I was  
18 running through that scenario in my mind. That's  
19 why I hesitated. If anybody feels that way, I'm  
20 good.

21 Okay. So we're now we're going to vote  
22 on question 2: Do you recommend that the maximum  
23 nonprescription single adult dose be limited to  
24 650 milligrams? Same choices as before.

25 MS. FERGUSON: Five people haven't voted,  
26 or didn't push their button.

27 (Discussion off the record.)

28 MS. FERGUSON: Okay. We're good. Thank

1           you.

2                   DR. NELSON:   Okay.   The results of the  
3   vote on the second question:   Yes, high priority,  
4   12; yes, 12; and no, 13.

5                   And now, as per Dr. Wolfe's  
6   recommendations, does anybody have any pertinent  
7   or pressing comments they feel should be entered  
8   into the record about why they voted no, in  
9   particular, or yes, or strongly yes?

10                  Yes, Dr. Benowitz.

11                  DR. BENOWITZ:   I'll comment because I was  
12   a person who voted no on the first one and yes on  
13   the second one.   I don't think that there's good  
14   everything that 4,000 milligrams is more toxic,  
15   and I think it may be of benefit, although it's  
16   not been demonstrated, but I think it is also true  
17   that the more pills you have available to abuse or  
18   take by mistake, the more likely it is, with a  
19   narrow toxic therapeutic ratio, that you'll take  
20   an excessive dose.

21                  You can always take three pills for each  
22   dose to get to 1,000.   So based on those  
23   combinations of arguments, I voted yes -- no and  
24   yes.

25                  DR. NELSON:   Dr. Chojkier.

26                  DR. CHOJKIER:   Well, in the first  
27   question, I voted strongly yes.   The reason is I  
28   don't believe that it's true that there is not

1 evidence of toxicity with 4 grams. There is a  
2 study published in JAMA, a very regarded journal,  
3 indicated patients that are normal, not taking any  
4 concomitant medication, on a standardized normal  
5 diet as inpatients, without any health problem,  
6 without liver problem, have -- 33 percent of them  
7 have three times upper limit of normal ALT. This  
8 is not the normal situation.

9 FDA would not allow a medication to  
10 continue like that. It would be a new IND.

11 So I don't think that it's true. That  
12 dose may not progress to acute liver failure -- I  
13 agree with you. But there is something happening  
14 there that is troubling, at least. And if that  
15 patient has an underlying liver disease or is  
16 taking more alcohol during that weekend because he  
17 has a cold and he has a party or something like  
18 that, maybe we will have the same situation that  
19 we have found in other unintentional liver  
20 toxicities.

21 So that's the reason why I think it will  
22 help.

23 DR. NELSON: Yes.

24 DR. STERGACHIS: Stergachis. And I voted  
25 strong yes, and in addition to the potential for  
26 reducing the total dosages taken per day, I was  
27 also influenced by that same JAMA article on the  
28 elevations in ALT that were four-fold associated

1 with 4 grams a day in otherwise healthy people.

2 DR. NELSON: Does FDA have any specific  
3 questions or issues they want raised at this  
4 point?

5 Does anybody else have any other  
6 comments?

7 Okay. I think it's worth going on to  
8 option 1b at this point, which is, as noted,  
9 somewhat related. If the OTC dose were reduced, I  
10 guess, would it be, you know, worth or valuable to  
11 switch the current higher dose of 500 milligrams  
12 to prescription status, either a 500-milligram,  
13 1,000 milligrams per dose, or 4 grams as the daily  
14 maximum dose?

15 So that's assuming that they lowered, as  
16 the results in the first two questions, the  
17 over-the-counter daily dose, or individual dose.

18 So, as before, I would like to take some  
19 discussion.

20 Dr. Olsen.

21 DR. OLSEN: Could I just ask a  
22 clarification? Would it require, if the person  
23 wanted to take one 500-milligram tablet, that  
24 would require a prescription? Or only if they  
25 were going to take 1,000 milligrams as one dose?

26 DR. NELSON: I would ask the FDA, but my  
27 reading of this is it's a 500-milligram tablet.  
28 There's no other way to get 500 milligrams. Is

that right? I mean, you couldn't cut a 325 easily into 500 milligrams.

DR. GANLEY: This is Charlie Ganley. I think that would be a correct way to think about it.

DR. NELSON: Dr. Vaida.

DR. VAIDA: I guess I have my question again about the 650, that -- just because it's an extended release, does that come into play here? So does that mean the 650 extended release goes off the market, or would be prescription? I just have that issue again about where that fits because it seems like, in the last question, we just acted like it didn't fit because it was an extended release, even dosed differently. So where does the 650 -- if we voted yes --

DR. GANLEY: Let me just try to clarify. The approval of that application was also based on what was already in the monograph in terms of the range of doses permitted. So if we're going to change the maximum daily dose and we're going to change the tablet strengths, it could potentially have an impact on that new drug application. Because that is -- you cannot market an extended-release formulation except under a new drug application. You cannot do it through the monograph for any products.

Okay. So there is a potential that that

1 would change if we would go with a lower daily  
2 dose under the monograph, and also change it so  
3 that the tablet strength is 325.

4 Again, that's based -- part of that  
5 approval is based on, you know, comparing the  
6 pharmacokinetics of an extended-release to  
7 immediate-release tablets, although I do believe  
8 they did some efficacy studies in that  
9 application. Okay?

10 But if we're going to change the OTC  
11 availability, it could impact on that application.  
12 I can't say what that change would be, but it  
13 could impact on it.

14 DR. NELSON: Thank you.

15 Dr. Gellad.

16 DR. GELLAD: I was curious, from the FDA,  
17 what's the approximate time it would take for a  
18 500-milligram pill to be -- would it be  
19 immediately available prescription status for an  
20 M.D. or a prescriber? Or how long would that take  
21 to be available?

22 DR. GANLEY: I think anything that --  
23 this is Charlie Ganley. Anything that would be  
24 done, we're talking, you know, years to get to.  
25 There would have to be some coordination between  
26 how we handle things for the OTC products. And if  
27 they were going to move to some prescription-type  
28 product, there would obviously have to be

1 coordination between that.

2 DR. GELLAD: I make the point because I  
3 think that there are probably cases in which --  
4 and the rheumatologist can speak to this more --  
5 where 1,000 milligrams may be useful, especially  
6 for reducing the number of pills someone has to  
7 take, especially the elderly and the -- in order  
8 to alternate it with Motrin or other methods for  
9 pain. So I guess that is a consideration in terms  
10 of --

11 DR. KWEDER: And let me clarify, though.  
12 We would take into consideration the coordination  
13 of the changes to the OTC with the availability of  
14 the Rx, and work with the sponsors as closely as  
15 possible to avoid that sort of big gap that I  
16 think you have some concerns about.

17 DR. NELSON: Thank you.

18 Dr. Kerns.

19 DR. KERNS: I -- earlier when I made my  
20 comments about making these decision out of  
21 context, I don't think anybody has considered the  
22 costs associated with these changes. I'm very  
23 concerned about a change that would burden an  
24 already strained healthcare system and patient  
25 burden by making something like 500 milligrams of  
26 Tylenol being a prescription. And -- so that's  
27 one concern.

28 And then the other related concern is I



1 think we already are hearing that the issue about  
2 unintended consequences is partly related to  
3 prescribing practices already about prescribers  
4 who are either ignorant or not practicing within  
5 reasonable standards of care and making decisions  
6 about prescribing combination medications that  
7 place patients at risk. This just further  
8 emphasizes -- underscores that problem.

9 DR. NELSON: Any other comments or  
10 discussion?

11 Dr. Engle.

12 DR. ENGLE: I just want to make sure I  
13 understand this. If -- you have to vote yes in  
14 order to have the 500 available; is that right?  
15 Am I understanding the question? Otherwise, the  
16 500 just wouldn't exist anymore.

17 DR. NELSON: I would defer to FDA on how  
18 to answer the question.

19 DR. GANLEY: It's Charlie Ganley. That  
20 could be a potential outcome. I think one of the  
21 problems, you know, that we're dealing with here  
22 is that this medication has been around for years.  
23 People take two tablets. And, you know, we would  
24 have to have discussions internally whether we  
25 would consider having a range of doses for an OTC  
26 product that ranged from 325 to 650 if we were  
27 going to lower the maximum dose.

28 The current monograph sort of allows for

1       that, where it would allow for a 500-milligram  
2       dose to be given one dose -- one tablet I think  
3       it's every three or every four hours. Okay. But  
4       you're asking us questions that we really can't  
5       answer.

6               I think our concern would be that if you  
7       have a 500-milligram tablet OTC and people are  
8       generally used to taking two tablets, that they're  
9       going to continue taking two tablets. And so we  
10      defeat the purpose of lowering the maximum  
11      individual dose if we were going to go to 650.  
12      Okay. So I think you're asking very good  
13      questions, and we can't necessarily give you  
14      the -- you know, the full answer now, but that's  
15      the best we can do.

16             DR. ENGLE: Because it's difficult to  
17      decide how to vote on this. Because you start  
18      thinking of the burden to the pharmacy and the  
19      burden on the patient to suddenly have to get a  
20      prescription, which means an office visit, so  
21      additional cost -- I'm struggling with that, you  
22      know, but I think the 500-milligram should be  
23      available, so it's hard --

24             DR. GANLEY: You understand what we've  
25      been struggling with --

26             DR. ENGLE: Yeah.

27             DR. GANLEY: -- for the last few years,  
28      then.

1 DR. ENGLE: Okay. Thank you.

2 DR. KWEDER: But I think, as a general  
3 approach to the question, to try and help you,  
4 remember that this one says, if the current  
5 dose -- if it were to come to pass that we lowered  
6 the total daily dose and perhaps the tablet size  
7 based on the first two questions, do you see a  
8 role for having prescription availability of the  
9 higher dose and maximum daily dosage?

10 I mean, I think that's one way to look --  
11 that's kind of how we think of that.

12 DR. NELSON: Dr. Lorenz.

13 DR. LORENZ: My way of thinking about it  
14 as well is that this is really just sending a  
15 signal that it's not as if people won't engage in  
16 unapproved uses of the 325-milligram tablets  
17 instead of taking three. And so I think -- you  
18 know, some of these things that we're concerned  
19 about are obviously going to be a negotiation.

20 But my understanding of the value of this  
21 is as a signaling function.

22 DR. NELSON: Dr. Gellad.

23 DR. GELLAD: Just a quick point that I'm  
24 not sure necessarily that if the 500 became  
25 prescription it would necessitate an office visit.  
26 I mean, I think that I personally would feel very  
27 comfortable prescribing something without  
28 necessarily needing to see the patient, especially

1 if it were Tylenol.

2 So I'm not sure, in terms of the burden,  
3 that I would agree that that's a particular  
4 burden.

5 DR. NELSON: The comment was made before  
6 about the way that nonprescription-strength  
7 ibuprofen is used with patients knowing that there  
8 is a prescription strength. So if the 325 was  
9 available and the patient knew that you could take  
10 1,000, even though we limited the dose to 650, it  
11 would seem analogous to taking three of those,  
12 ultimately, just like it would be to take 800  
13 milligrams of ibuprofen. Not necessarily that  
14 that's the right way to do things, but that's  
15 inevitably what would happen.

16 Dr. Markman.

17 DR. MARKMAN: John Markman. I would just  
18 underscore Dr. Kerns' point about how making this  
19 prescription would really increase a barrier to  
20 care, make access to care more difficult. And  
21 just to keep in mind that among patients with  
22 chronic pain, the elderly are one of those  
23 populations that are most at risk for being  
24 undertreated for pain.

25 DR. NELSON: Dr. Landis.

26 DR. LANDIS: Yes. I would almost speak  
27 against it, and I'm wrestling -- like Jan is a  
28 pharmacist -- because I don't think we need to

1       burden the system by putting it on prescription.  
2       There is no benefit to the patient at that point.  
3       Yet again we're in a system where we don't have a  
4       lot of options.  It's either prescription or  
5       nonprescription.

6               And I'll reiterate what I said before.  
7       If we had another option -- and, again, FDA is  
8       tight on this -- where there was a pharmacist-only  
9       category, that would certainly help put a drug  
10      such as this here in a category that would allow  
11      some oversight as far as what the patient is  
12      getting.

13             It is a burden for seniors that are out  
14      there.  They need to have what is necessary for  
15      them to have the dose and the pain relief.  So we  
16      can't tie their hands to this, and that's part of  
17      the reason I voted no on 1 and 2 previously,  
18      because I think we have to have it available and  
19      we have to look at, what are the consequences of  
20      what comes out of this meeting for those that are  
21      out there?  And the burden -- cost is going to be  
22      to the consumers.

23             DR. NELSON:  Okay.  Last comment,  
24      Dr. Farber.

25             DR. FARBER:  Just one thing about access.  
26      As an internal medicine physician, I see a lot of  
27      elderly patients, and I agree that they need  
28      access to pain relief.  However, I want to know

1 when my patients are hurting, because there may be  
2 other measures that I want to take with them.

3 So I don't think that it's necessarily a  
4 bad thing that it be a prescription strength.

5 DR. NELSON: Okay. To the question -- to  
6 the vote. If the current doses of nonprescription  
7 products are lowered, do you recommend that the  
8 current maximum dosage of acetaminophen -- that  
9 is, two times 500 milligrams -- be switched to  
10 prescription status?

11 A, yes highly; B, yes; and C, no. Vote  
12 now.

13 The voting results: Eight said yes, high  
14 priority; 18 said yes; and 11 said no.

15 Anybody that would like to comment about  
16 some of their reasoning at this point?

17 Dr. Kerns.

18 DR. KERNS: Yes. It seems to me that if  
19 the FDA made a decision, based on these -- the  
20 data, and other data, to eliminate -- or to lower  
21 the single-unit dose and daily maximum dose, it  
22 would be based on a sound judgment about the  
23 efficacy and risk, and making it available by  
24 prescription, putting it in the hands of people  
25 that are already not prescribing well, wouldn't  
26 have any particular benefit. That's why I voted  
27 no. I think the drain on the healthcare system  
28 that's already enormously overstrained would be

1 enormous.

2 DR. NELSON: Dr. Omogui.

3 DR. OMOGUI: I voted yesterday, high  
4 priority, because we already have existing models.  
5 Pepcid AC is available OTC as 20 milligrams and,  
6 as prescription strength, 40 milligrams. We have  
7 the same thing for ibuprofen, 200 milligrams OTC  
8 and 800 prescription.

9 So I think our existing models have  
10 worked, and we can apply the same thing in this  
11 situation.

12 DR. NELSON: Yes, Dr. Raja.

13 DR. RAJA: I just wanted to reiterate  
14 some of the discussion that's gone in. As a  
15 practitioner of pain medicine, I think the option  
16 of having the higher dose for those subset of  
17 patients who need the higher dose, but as a  
18 prescription offers the compromise of having it  
19 available, but also having a face-to-face  
20 discussion with the patient on the potential  
21 toxicity allows a compromising solution.

22 DR. NELSON: Thank you.

23 FDA? Any other questions or issues?

24 I think, rather than go on to the next  
25 question, we should probably take our lunch break  
26 now. We'll meet back at 1:10, in about one hour.  
27 Thank you. And please remember not to discuss  
28 these issues over lunch.

1 (Whereupon, at 12:11 p.m., a lunch recess  
2 was taken.) AFTERNOON SESSION

3 (1:12 p.m.)

4 DR. NELSON: Okay. It's ten after.  
5 We're going to get restarted. Thank you.

6 So we are about one-third of the way  
7 through the questions. We're going to pick up on  
8 our sheet, on our yellow pages on page 4, from  
9 option -- paper option 2, to establish pack size  
10 limits for over-the-counter acetaminophen  
11 products. And the question that we're going to be  
12 ultimately answering is, do you recommend that  
13 pack size limits be implemented for  
14 nonprescription acetaminophen products?

15 And I'd like to have some discussion for  
16 a few minutes before we vote.

17 Dr. Kramer.

18 DR. KRAMER: I have a question for FDA on  
19 this one, which is, can the committee specify  
20 that, if there were a pack size limit that it  
21 should apply to salicylates and NSAIDs as well, to  
22 avoid inadvertent unintentional impact on safety?

23 DR. GANLEY: This is Charlie Ganley. I  
24 think if you want to make that recommendation, you  
25 can also do that.

26 DR. KRAMER: And could you give us the  
27 information? Someone said something in the  
28 hearing yesterday that you could go to your local



1 Costco, or a place like that, and get huge  
2 bottles. Could someone specify how large the  
3 largest bottle that's sold -- are there bottles of  
4 Tylenol of 500 to 1,000 tablets? Could someone  
5 clarify so we know what the situation is?

6 DR. NELSON: We're hearing 500. Okay.  
7 Anybody want to say 1,000?

8 Dr. Kuffner?

9 DR. KRAMER: The maximum size of any  
10 manufacturer.

11 DR. KUFFNER: The maximum size of any  
12 manufacturer -- for Tylenol, it's 325. For --  
13 there are some store brands that's a 1,000 pill  
14 count.

15 DR. KRAMER: 325-milligram?

16 DR. KUFFNER: 325 pills is the largest  
17 for Tylenol, but there are some store brands  
18 that's up to 1,000.

19 DR. KRAMER: And is it a coincidence that  
20 the number of 325 is the same as the strength --  
21 used-to-be strength of tablets?

22 DR. KUFFNER: I think that's probably a  
23 coincidence.

24 DR. NELSON: Of course it is.

25 Are there -- one comment that I had was  
26 that -- you know, the UK experience is  
27 interesting, but one thing to keep in mind is that  
28 the package size limitation actually still puts an

1 amount of drug into a single packet that, for most  
2 adult human beings, would be potentially fatal, so  
3 there's still 16 grams in a packet.

4 So if the intent is to limit the  
5 intentional overdose from occurring, the packet  
6 size restriction would have to be greater than  
7 that. I mean, most adults would probably have to  
8 have less than 10 grams, typically, to not be very  
9 concerning an overdose.

10 Ms. Landis.

11 DR. LANDIS: Again, this is, I guess, a  
12 question in regards to the market that's restrict,  
13 because I don't understand it. If it's a  
14 non-pharmacy place -- gas station or maybe a  
15 supermarket or whatever where there's a  
16 non-pharmacy -- are there any limitations here in  
17 the U.S., or can they sell that 500-size bottle?  
18 And has there been anything -- have they looked  
19 at, possible, restricting the sizes for that?

20 DR. NELSON: Are you asking that to  
21 somebody specifically or just bringing it up?

22 DR. LANDIS: Well, either to industry --  
23 I assume that they're the ones that are probably  
24 going to be the most knowledgeable as far as what  
25 they can put into these non-pharmacy places.

26 DR. SUYDAM: As I understand it, there  
27 are no restrictions. However, you will find the  
28 big sizes only in the big-box stores like Costco

1 and Sam's. That's where you'll find the  
2 1,000-tablet bottles or the 500-tablet bottles.

3 In the convenience stores, you usually  
4 get, like, a two-pack or a six-pack or very small  
5 amounts.

6 DR. NELSON: Actually, Dr. Wolfe was  
7 next.

8 DR. WOLFE: One of the yet-unexplained  
9 differences, other than methodology of  
10 interviewing people between the UK and here was  
11 they're 90 percent intentional, and one plausible  
12 reason why there wasn't a greater decrease in  
13 liver toxicity there -- I mean, they said -- some  
14 said that it was as much as 30 percent; some said  
15 it was 10 percent or zero or whatever -- is if  
16 most of the audience is intentional, then, as  
17 you're suggesting, they can overcome some of that.

18 Here it is thought that it's not 90  
19 percent intentional, but I think that between  
20 getting rid of the 325 or 1,000 pills per bottle  
21 and trying something like this -- there's no  
22 downside of the decreased packet size. There's  
23 either -- it may not have as much of an effect,  
24 particularly in a country where it's mainly  
25 intentional -- or it will have a small effect.

26 And, again, as I was sort of saying this  
27 morning, this is another element to be added to  
28 four or five others, each of which may have some

1 incremental effect on improving the situation.

2 DR. NELSON: Thank you.

3 Dr. Omogui.

4 DR. OMOGUI: I think there are two  
5 different problems between the UK and the U.S., so  
6 I'm not sure we should address a problem that  
7 really does not exist right now here in terms of  
8 limiting this packet size.

9 If most of the poisoning here is  
10 unintentional, then creating solutions for  
11 problems that don't exist may not seem applicable.

12 DR. NELSON: Thank you.

13 Dr. Farber.

14 DR. FARBER: Neil Farber, UC San Diego.  
15 There is one downside to think about. We were  
16 talking about elderly before and the difficulties  
17 elderly might have in getting pain relief. This  
18 is one area where it really might affect the  
19 elderly. For example, someone with osteoarthritis  
20 who has to take several acetaminophen per day  
21 would end up having to go to the store, try and  
22 get to the store, and buy packets of acetaminophen  
23 every day, or every other day, or something on  
24 that basis, if we really limited it. So that  
25 would be my one concern.

26 DR. NELSON: Dr. Day.

27 MS. DAY: Thank you. I was struck by  
28 that 90 percent intentional figure for the UK as

1 well, and with all due respect to our colleagues  
2 in the UK, I don't exactly believe it until we  
3 know how it was measured.

4 So there, if a person says, oh, I had big  
5 pain, I needed big medicine -- and then gave  
6 themselves more, that's intentional. But it  
7 doesn't mean -- it's not our interpretation, when  
8 we think of intentional for self-harm.

9 So they weren't using the same  
10 terminology with us, and I suspect that maybe the  
11 coding of patients' responses might have been  
12 different. So I wouldn't rush to conclude too  
13 much about the 90 percent until we know more.

14 DR. NELSON: Dr. Brull.

15 DR. BRULL: Sorin Brull. On the same  
16 venue, I was also struck by the difference between  
17 the UK and the U.S. experience, and I would  
18 perhaps like to offer yet another explanation for  
19 that.

20 The intended versus unintended, the 5  
21 [sic] percent suicide supposed in the UK versus up  
22 to 50 percent in the United States -- it's  
23 possible that the apparent rates are different  
24 because of the different healthcare systems. In  
25 the U.S., it is possible that the physician may  
26 actually try to protect the patient from the  
27 stigma of suicide, or try to protect their ability  
28 to get insurance, life insurance, health

1 insurance, if he or she is labeled as a suicide  
2 victim. So that's another explanation.

3 DR. NELSON: Dr. Chojkier.

4 DR. CHOJKIER: Mario Chojkier, UC San  
5 Diego. I agree with Dr. Farber, a colleague from  
6 the university, that restricting the size package  
7 for elderly with osteoarthritis or similar pain  
8 problems will be a difficulty.

9 But from a package of 32 to a package to  
10 1,000, there is quite the room. I'm not  
11 advocating -- I wouldn't advocate to make it 32,  
12 but certainly I believe that it's a wrong signal  
13 for teenagers or whatever showing 1,000 tablets of  
14 a medication. It gives the impression that this  
15 is like candy to anybody.

16 I'm not a psychologist, but I think that  
17 that would look to me, if I would be located in a  
18 medical field -- so I think that somewhere the FDA  
19 should consider putting a cap on the -- limit on  
20 the number of tablets, whether it's 100 or  
21 something that would be sensible, it would be  
22 sufficient for an elderly patient.

23 DR. NELSON: Dr. Griffin.

24 DR. GRIFFIN: I would just like to say  
25 that I was unconvinced by the data from the UK  
26 that -- these were all before/after studies with  
27 no control for temporal trends in suicide, which  
28 there are temporal trends in suicide. And so I

1 think the data that this intervention worked was  
2 very unconvincing. And I don't think there's  
3 strong evidence that this is part of the problem  
4 here. So I think it would be fixing something  
5 that we're not sure is part of the problem, and  
6 also with an intervention that really is -- I'm  
7 unconvinced, anyway, that it worked.

8 DR. NELSON: You know, I am actually a  
9 little -- it's Lewis Nelson. I'm pessimistic  
10 about its helpfulness for the reasons that we  
11 heard from the two UK speakers, and their  
12 disagreement upon what actually transpired over  
13 there, which I thought was pretty interesting,  
14 because you'd think there would be a more  
15 clear-cut trend.

16 But what also troubles me is the fact  
17 that concomitant with the reduction in the pill  
18 size was a pretty aggressive educational campaign  
19 about, you know, the dangers of acetaminophen, or  
20 paracetamol, in overdose. And despite those two  
21 things going on simultaneously, it didn't really  
22 seem to have a tremendous impact like you'd expect  
23 it to, on the incidence of acute overdose.

24 You know, it's probably all we can really  
25 get out of their information, but it didn't seem  
26 to have the effect we'd like.

27 Anybody else have any comments?

28 Dr. Brull.

1 DR. BRULL: Sorin Brull. since you  
2 brought up the subject of education, I think we've  
3 heard from a couple of people who sort of said  
4 that education probably is pretty far down the  
5 line and may not be very helpful. On the other  
6 hand, we have very good examples of educational  
7 processes that worked quite well.

8 And one of the things that might be  
9 considered, for instance, is the education of --  
10 since the greatest proportion of at-risk  
11 population is the very young, the adolescents, the  
12 teenagers, maybe starting some educational  
13 processes in high schools and colleges maybe a  
14 thought.

15 DR. NELSON: Dr. Raja.

16 DR. RAJA: I just wanted just to remind  
17 the data that was presented by Dr. Dargan, that  
18 even though packet sizes were limited, it did not  
19 prevent people from getting multiple packages.

20 DR. NELSON: Yes. He's not here to  
21 answer, but in one of his slides he showed that he  
22 sent some medical students out and specifically  
23 was able to buy multiple packages in varying sizes  
24 fairly easily.

25 Dr. Wolfe.

26 DR. WOLFE: The way the question is  
27 worded doesn't mandate that we vote to go down to  
28 16 or 32. I think it mandates a limit, and I



1       certainly agree with what Dr. Farber and others  
2       have said about particularly older people.

3               On the other hand -- or on the same hand,  
4       really -- the educational value of announcing  
5       that, from now on, you're not going to be able to  
6       buy this drug in a bottle of more than 50 or 100  
7       or whatever, as opposed to it's so safe that we  
8       can sell 1,000 at a time -- and the message that  
9       goes out with that kind of allowance of sale is,  
10      you shouldn't worry about this stuff. And it's an  
11      anti-educational message.

12              So I think that the educational  
13      implication of even some reasonable limitation on  
14      the maximum unit of sale would be very helpful.

15              DR. NELSON: Okay. Two more comments.

16              Dr. Vaida.

17              DR. VAIDA: Probably just going along  
18      with what Dr. Wolfe said, too. I look at this as  
19      really open-ended, that the FDA is going to -- and  
20      maybe there could be a 500-tablet OsteoPak or  
21      something that you could get behind the counter or  
22      whatever. But this is pretty open-ended, and I  
23      wasn't real convinced with the UK data, but I  
24      don't know if this is saying that we're going to  
25      go down to 32 or 16.

26              DR. NELSON: Dr. Landis.

27              DR. LANDIS: Yes. I think, if we allow  
28      the 1,000 size, the big size, to be in

1 non-pharmacy areas, we send a message to the  
2 public that says this is a safe medication; you  
3 can just buy it next to, you know, the ten tubes  
4 of toothpaste or whatever.

5 I think that we have to send a message  
6 that, you know, there is problems with this  
7 medication. I don't think we should limit it to  
8 the small sizes. I think the UK showed that that  
9 wasn't there. But I think there should be  
10 consideration from the FDA as far as, in a  
11 non-pharmacy location, what is the size, what is  
12 the strength that we have available to people.

13 DR. NELSON: Dr. Benowitz.

14 DR. BENOWITZ: I just point out that if  
15 the dose is cut down to 325 milligrams per tablet  
16 and the daily dose is 3250 per day and you have  
17 chronic arthritis, a month's supply is 300, and  
18 I -- you know, if I prescribe to a patient, I hate  
19 to prescribe less than a month's worth. So the  
20 bottles can't get too small if they're going to be  
21 the parameters.

22 DR. NELSON: Dr. Kweder.

23 DR. KWEDER: I just wanted to point out  
24 that this question is a little bit open-ended, for  
25 several reasons. One is it's exactly what  
26 Dr. Benowitz said. It's -- one of the  
27 considerations that we've asked you to consider is  
28 how would you determine an appropriate package

1 size and what kind of restrictions are you  
2 thinking we should put on consumers who are  
3 seeking to have a supply on hand?

4 The other piece of this is -- and it was  
5 in the background package, but I did want to  
6 remind people that this is one of the changes that  
7 may require some additional steps to achieve  
8 because it is not clear at this point in time, you  
9 know, which component of our regulatory authority  
10 we would be able to employ to effect this change.

11 This is not difficult -- is not so  
12 difficult to do for a prescription product, but  
13 the products that we have on the market today that  
14 are nonprescription that have package size  
15 limitations are there for other reasons, not  
16 because of FDA necessarily.

17 DR. NELSON: Okay. Thank you. It's time  
18 to vote.

19 Please.

20 DR. JOHNSON: Could I just ask, with  
21 Dr. Dargan back, one thing that FDA learned in the  
22 background for this that might be worthwhile, just  
23 before the committee votes, is to understand the  
24 difference between suicide events in the UK and  
25 here. There's different modes and it's a  
26 different professor.

27 DR. DARGAN: I think -- there's a clear  
28 difference in the unintentional to intentional

1 ratio in the -- not just in the UK, but in Europe  
2 as a whole, and Australasia, to North America, and  
3 it's difficult to understand what the background  
4 to that is, but certainly in terms of suicidal  
5 behavior in the UK, there's a very much lower  
6 proportion of, for instance, violent suicides, and  
7 a much greater proportion of drug-related  
8 poisoning responsible for suicide, and so  
9 potentially that will inflate or -- inflate the  
10 number of intentional poisonings with drugs, and  
11 available drugs such as paracetamol or  
12 acetaminophen.

13 And I think there's reasonably sort of  
14 conclusive data from the UK, elsewhere in Europe  
15 and Australasia, that 90 to 95 percent of  
16 significant acetaminophen poisoning with  
17 hepatotoxicity is related to intentional poisoning  
18 and not to unintentional poisoning. I think  
19 that -- maybe the point that Sue was getting to is  
20 the difference in the suicidal behavior and the  
21 choice of method in Europe, potentially, to North  
22 America, and the greater use of drugs rather than  
23 potentially violent methods.

24 DR. NELSON: Do you want to re-ask your  
25 question?

26 MS. DAY: Yes. Can you say, does  
27 intentional mean necessarily suicidal? There  
28 might be an intentionality that, if X number of

1 pills works well, 2X will be more, 3X will be  
2 more -- so there's an intentionality to really  
3 treat some kind of pain. Is that the same thing  
4 as suicidality? How is -- how is intentional  
5 asked and coded from the data that patients give  
6 you?

7 DR. DARGAN: I mean, clearly, that will  
8 be different across different data sets and across  
9 different studies, but in terms of the way that it  
10 will be coded in the UK, it would be around  
11 intentional para-suicidal ingestion rather than  
12 patients taking repeated doses for significant  
13 pain.

14 So, you know, the unintentional and the  
15 coding of unintentional ingestions will be  
16 repeated -- generally repeated supra-therapeutic  
17 ingestions whereas the intentional ingestions will  
18 be single, large, acute ingestions associated  
19 with, you know, an intent to do harm as opposed to  
20 being taken for pain.

21 MS. DAY: So if a patient thinks, I have  
22 big pain, I'm taking big medicine, that is  
23 interpreted as suicidal, because it's one-time  
24 dosage?

25 DR. DARGAN: No. No.

26 MS. DAY: All right. Just to clarify.  
27 Thank you.

28 DR. NELSON: Dr. Lee, did you want to

1 make a comment?

2 DR. LEE: I think Paul has basically  
3 covered it, but in the U.S., as I showed on my  
4 slide yesterday, there are clearly two types, and  
5 they are about equal in numbers. The  
6 unintentional are taking it over several days,  
7 over several days, for a specific cause for pain,  
8 and they deny suicide.

9 Now, there may be a couple of people on  
10 the edges who were taking it chronically, but then  
11 upped the dose on the last day. But I don't think  
12 the hepatologists are hiding these real suicides.

13 The other people are taking a single time  
14 point ingestion. They admit to suicidal attempt,  
15 and those are really the specific features. And  
16 they don't typically have a cause of pain.

17 DR. NELSON: Good. Now, if I could point  
18 out as well that those -- and you gave this data  
19 yesterday, but those that take a single overdose  
20 and present to healthcare have a much better  
21 outcome, typically, than those who get  
22 therapeutically poisoned, often because of delay  
23 to presentation.

24 Okay. I think it's time to vote. So the  
25 question again, you'll remember, is, do you  
26 recommend that pack size limits be implemented for  
27 nonprescription acetaminophen products? A is yes,  
28 highly; B is yes; and C is no.

1                   The voting result: Yes, high priority,  
2                   2; yes, 15; and no, 20.

3                   Would anybody like to enter a comment  
4                   specifically explaining the reason they voted the  
5                   way that they did?

6                   Dr. Engle.

7                   DR. ENGLE: I just wanted to make the  
8                   point that while I would have no problem  
9                   restricting the larger sizes, the big ones, the  
10                  1,000s or 500s, to pharmacies or that sort of  
11                  thing, at least in the patient populations that I  
12                  deal with in our socioeconomic environment, we  
13                  have a lot of families that are multi-generational  
14                  that are living together, and there's multiple  
15                  parents, multiple children -- or older people that  
16                  would use the Tylenol, or the acetaminophen, so  
17                  they need those large package sizes to be able to  
18                  treat the entire family.

19                  So even though I voted no, I'm not  
20                  necessarily against limits in the really large  
21                  sizes. But we have to be cognizant of these  
22                  families that live together that are large, that  
23                  need that many dosage forms.

24                  And then also in rural environments where  
25                  it's very difficult to get to the pharmacy, and  
26                  for reasons that have already been outlined with  
27                  osteoarthritis and all that, I think we have to  
28                  keep that in mind as well.

1                   So if FDA decides to move forward, I hope  
2 they consider those points.

3                   DR. NELSON: Dr. Kramer.

4                   DR. KRAMER: I'd just like to say that I  
5 think the arguments that have been expressed by  
6 other members about the really negative or wrong  
7 message that's sent by these very large containers  
8 in the big-box stores makes me disappointed that  
9 the vote makes it sound like the committee didn't  
10 support that, and yet I thought I heard individual  
11 comments, just like we just heard, that would  
12 suggest that. So I hope the FDA doesn't consider  
13 this no vote to mean that we support selling 1,000  
14 acetaminophen tablets in Costco.

15                  DR. NELSON: Dr. Morrato.

16                  DR. MORRATO: Elaine Morrato. I'd second  
17 that. That's why I voted very highly for this  
18 one, because I was thinking of it in that context  
19 of the 1,000 tabs, and do you really need that in  
20 a bottle, as opposed to -- not the UK model of  
21 going down to 32, so...

22                  DR. NELSON: Dr. Olsen.

23                  DR. OLSEN: Yes. Olsen. I also voted  
24 with high priority for exactly the same reason.  
25 I'm giving kind of an open statement that it  
26 should be looked at very carefully, and the exact  
27 amount will have to be decided, and I think that  
28 should have high priority.



1 DR. NELSON: Dr. Day.

2 MS. DAY: I would just like to comment on  
3 Dr. Kramer's comment. I don't see this as a no  
4 vote. I see this as a split vote. Two were yes  
5 with high priority; 15 were yes. So that's 17  
6 versus 20. So I interpret this as a split vote,  
7 not a no vote.

8 DR. NELSON: Okay. Yes, Dr. --

9 DR. STERGACHIS: -- Stergachis. Just a  
10 quick comment. I did the same math that  
11 Dr. Benowitz did, and there should be allowances  
12 made for people who use acetaminophen on a chronic  
13 basis in any size limit considerations.

14 DR. NELSON: Dr. DeNisco.

15 DR. DeNISCO: It was -- I changed my vote  
16 when I realized that this would not be a 32  
17 blister pack, that would probably be \$7.00 for 32  
18 pills, but that certainly the 1,000 bottle  
19 tractor-trailer case delivery from the big-box  
20 store, that is unnecessary, too. But a, you know,  
21 500 or 300 would be something reasonable. But  
22 going to blister packs, I would definitely be  
23 against going to very expensive, very difficult to  
24 open blister packs.

25 DR. NELSON: And I'm personally not  
26 convinced -- it's Lewis Nelson. Unless you're  
27 going to bring the bottle size down to something  
28 that makes it almost un-overdosable, it matters

1       whether they're available in 100 or 1,000 -- it  
2       seems that -- I don't think there's any data to  
3       support the difference in clinical outcomes if you  
4       take 20 grams or 40 grams or 60 grams. I mean,  
5       once you get above that critical threshold, you've  
6       just taken too much. You need to be treated; you  
7       need antidote therapy, or not.

8               But I think that -- the reason I voted no  
9       is because I think that the concept of the size  
10      limitation that you had in mind probably wouldn't  
11      bring it down to be small enough -- whether you  
12      have 1,000 or 500 or 300, it doesn't seem to  
13      matter, in my mind.

14             Dr. Jenkins -- I'm sorry. Dr. Covington.

15             DR. COVINGTON: Just recalling that  
16      sometimes the strength of our opinions is  
17      inversely proportional to the quality of our  
18      data -- and we have not heard one shred of data to  
19      suggest that people who overdose shop at Costco.  
20      I mean, we have fantasies that there's something  
21      dangerous or that we're giving a bad message, but  
22      at this point, it is just a fantasy; we have no  
23      data.

24             DR. NELSON: Okay. Last comment.

25      Ms. Landis.

26             DR. LANDIS: I think this question is  
27      really worded wrong, and I think if it had been  
28      given to us maybe in a little bit different

1 writing, that the numbers would be different on  
2 the board. I'm hearing a lot of people who are  
3 concerned about large sizes in, say, the Costco or  
4 wherever, where it's a non-pharmacy, the message  
5 that we send to the public, say, versus where it  
6 would be -- have a healthcare provider that was  
7 there to kind of assist with it.

8 So, you know, for the same reasons that  
9 people voted no, I voted yes. So I think a lot of  
10 us were on the page; we're just not sure how to  
11 vote because we're seeing -- we don't like the  
12 high end, but we don't want to restrict the low  
13 end.

14 DR. NELSON: Okay. Thank you.

15 Let's move on to the next option,  
16 option 5a, and that option is to eliminate  
17 nonprescription acetaminophen combination  
18 products.

19 And the question we'll be voting on is,  
20 do you recommended eliminating nonprescription  
21 acetaminophen combination products.

22 So, some discussion. Dr. Engle

23 DR. ENGLE: While it sounds like a good  
24 idea, possibly, to eliminate the combination  
25 drugs, because you can always take them separately  
26 and all that, I just want to make the point that  
27 there are some combination drugs that are not --  
28 that you can't duplicate. And the example I'm

1 going to use -- I'm going to just use one, because  
2 of time -- is Excedrin. Excedrin is 250  
3 milligrams of acetaminophen, 250 of aspirin and 65  
4 of caffeine. You can't buy those components  
5 separately.

6 So in the case of these folks who have  
7 headaches and migraines who really rely on that  
8 product, if we took it off the market, they have  
9 no alternative.

10 So I just want people to think about  
11 that, as you vote on this, that not all  
12 combination drugs -- you can't duplicate them all  
13 in single-entity products necessarily.

14 DR. NELSON: Thank you.

15 Dr. Kerns.

16 DR. KERNS: I just want to remind the  
17 panel that we heard virtually -- we were provided  
18 with virtually no information that could help  
19 inform this, other than information about the  
20 number of deaths or acute liver failure associated  
21 with unintentional ingestion of toxic quantities.  
22 We didn't hear anything about what these  
23 medications are, what their purpose are, what  
24 their efficacy are, how they play out in the  
25 broader market, et cetera.

26 DR. NELSON: Dr. Farber.

27 DR. FARBER: We do have a little bit of  
28 data, although it's extrapolated. We know that

1 the number of cases of people using multiple  
2 preparations with acetaminophen are small, but  
3 there are a number of people who do not understand  
4 the labeling and who do take multiple medications  
5 with acetaminophen and have overdosed that way.

6 The other thing is that if you look at  
7 the data on -- I agree that some of the  
8 medications cannot be replaced, and basically I  
9 think the FDA would have to look at each  
10 individual medication to see if it's something  
11 that can't be replaced and, therefore, would need  
12 an NDA, I guess, but would need to remain on the  
13 market.

14 But there are a lot of medications -- for  
15 example, cold and flu preparations -- where the  
16 need for acetaminophen is actually fairly small.  
17 If you look at the data presented by some of the  
18 manufacturers, only about half -- maybe a little  
19 more -- about 40, 45 percent of patients didn't  
20 have anything that acetaminophen would be good for  
21 in terms of that particular symptom complex that  
22 they had. And yet they have to take it if they're  
23 taking that particular preparation.

24 So I think we need to think about that on  
25 the other hand.

26 DR. NELSON: Thank you.

27 Dr. Omogui.

28 DR. OMOGUI: Again, I feel we should

1 develop a solution for a problem that exists.  
2 Based on the data that was provided, the  
3 combination OTC medications really contributed  
4 very little to the problem of acetaminophen  
5 poisoning. It was a very, very minor percentage.  
6 So I really don't see a problem that exists with  
7 them, and possibly because the amount of  
8 acetaminophen in these combination products is  
9 definitely much less than those in the  
10 single-agent products.

11 But there wasn't much of a problem, so I  
12 don't think we should be addressing a solution for  
13 a problem that's not there.

14 DR. NELSON: Dr. Wolfe.

15 DR. WOLFE: With all due respect to the  
16 Excedrin headache, I remember when they started  
17 advertising this, they were sort of a product  
18 looking for a kind of headache. I think that  
19 people -- the unique thing is the caffeine, to be  
20 sure, and people can drink a cup of coffee, not  
21 decaffeinated but regular.

22 I think that most, if not all -- most of  
23 these over-the-counter combination preparations,  
24 which do make up -- I think it was 10 percent of  
25 the fatalities -- it was not a tiny number; it  
26 wasn't the majority, but 10 percent -- people who  
27 unwittingly are taking two or more  
28 acetaminophen-containing products are almost by

1 definition taking ones that are not pure  
2 acetaminophen -- or one of them, at least, is not  
3 pure acetaminophen.

4 And so I think that aside from the  
5 questionable efficacy -- if you have a cold, you  
6 should treat one symptom. The one symptom may be  
7 if you're got your nose plugged up, you need some  
8 nose spray or nose drops or something like that --  
9 but the number of people -- this is sort of  
10 extending a little bit of what Dr. Farber was  
11 saying. The number of people who take these  
12 multiple-ingredient products, not just  
13 acetaminophen-containing, but any that actually  
14 have most, or even all -- or even most of the  
15 symptoms is small. This is a marketing packaging  
16 thing.

17 The FDA's review of over-the-counter  
18 drugs was by ingredient, not by product. And if  
19 the ingredient was found to be safe and effective,  
20 it's allowed on.

21 And the companies have taken a relatively  
22 small number of ingredients and created thousands  
23 and thousands of over-the-counter products that  
24 are grossly oversold.

25 So I think that -- since we're focusing  
26 on over-the-counter products, I would strongly  
27 support the idea of getting rid of -- there might  
28 be an exception. I think the default would be,

1 get rid of them, and if there's one where there's  
2 really an unequivocally important unique benefit,  
3 maybe an exception could be made.

4 DR. NELSON: Thank you.

5 Would you like to make a brief comment?

6 DR. SUYDAM: Mr. Chairman, if I could --  
7 slide on, please.

8 To -- I'm sorry. To Dr. Farber's  
9 comment. I think the data that we showed showed  
10 that on the first two days you have 62 percent and  
11 63 percent of people who have the symptom of a  
12 headache in the first two days of a cold, which  
13 then drops off. But for the first few days,  
14 having a combination product would, in fact, help  
15 treat that symptom.

16 And if I could, respiratory products that  
17 are combination products only have pain relievers  
18 in them about 43 percent of the time. So  
19 combination products do not always have pain  
20 relievers.

21 DR. HERTZ: Is there any evidence to  
22 suggest that these individuals change their  
23 combination product after their headaches resolve?

24 DR. SUYDAM: I'm sorry. Who's -- I'm  
25 sorry. We don't have that data in this study.

26 DR. FARBER: Neil Farber, UC San Diego.  
27 The only thing I would say is that, first of all,  
28 in terms of the headache that's seen, basically



1       there's two components of that. First of all, as  
2       I said, it's about 40 -- okay, so 48 percent --  
3       I'm sorry, 38 percent who do not have a headache  
4       at the beginning. So it's about 40 percent of  
5       people not having a headache and yet perhaps  
6       getting acetaminophen for something that they  
7       don't need it for.

8               In addition, although the -- 62 and 63  
9       percent have headache at day 1 and day 2, we don't  
10      know the intensity of the headache or that they  
11      needed any medication for that headache at that  
12      time. So --

13             DR. SUYDAM: We do know that, from  
14      studies, that people tend to buy their products  
15      based on their symptoms. So they will look for --  
16      slide on.

17             If you'll see this -- from a study that  
18      was done by Pegus in 2007, you'll see that, in  
19      general, people are quite familiar with -- very  
20      familiar with the list of -- the part of the label  
21      that lists the active ingredients, and then are  
22      quite familiar with also the symptoms that it  
23      treats.

24             So the data is showing people treat to  
25      symptoms.

26             DR. FARBER: Is this self-report?

27             DR. SUYDAM: This is self-report, yes.

28             DR. FARBER: So -- but we've also seen

1       that, based on this, that patients, although they  
2       reported that they knew what they were buying it  
3       for, and the symptoms and the medications, that  
4       they actually didn't know.

5               DR. NELSON:   Okay.   Thank you.

6               Dr. Benowitz.

7               DR. BENOWITZ:   A concern that I have with  
8       combinations are more the ones that people might  
9       be taking for protracted periods of time.   And the  
10      Excedrin example is actually one that bothers me a  
11      lot because here you have people with migraine  
12      headaches taking caffeine.   When they stop their  
13      caffeine, their migraine headache gets worse.  
14      They keep on taking this.   They're taking some  
15      other kind of pain medications.

16              I don't have really strong feelings about  
17      combinations in general, but I really feel that  
18      caffeine with acetaminophen is a bad combination.  
19      And I don't know if we can be selective about what  
20      we can get rid of, but I would certainly be in  
21      favor of getting rid of caffeine/acetaminophen  
22      combinations.

23              DR. NELSON:   Dr. Markman.

24              DR. MARKMAN:   I'd like to underscore  
25      Dr. Benowitz's point.   We heard yesterday from one  
26      of the experts in headache, actually, and I think  
27      something that many of us know who take care of  
28      headaches acutely is that multi-modal or multiple

1 mechanisms of actions in the acute setting can be  
2 very effective and can reduce the amount of  
3 medication needed, analgesic medication.

4 But to Dr. Benowitz's point, which I  
5 think is really an important one, in the chronic  
6 setting, it can lead to a more attenuated headache  
7 pattern, also known as medication overuse  
8 headache, which is increasingly refractory to  
9 treatment -- is really a separate syndrome in and  
10 of itself with even highly rates of disability  
11 oftentimes than the acute ones.

12 So I think it's important -- again, not  
13 to necessarily look at this in the framework of  
14 eliminating these products from the market, but  
15 just to know that, you know, we're asking a  
16 question here which I think has different  
17 implications for the acute problem versus for the  
18 chronic administration.

19 DR. NELSON: Dr. Watts.

20 DR. WATTS: I think there's some pretty  
21 good data that, unlike our British components, we,  
22 as Americans, can't seem to get the dose right on  
23 a single product, and now you're asking us to take  
24 a combination product, break it into four, and get  
25 four doses right. I'm not convinced we're not  
26 trading one problem for yet another.

27 DR. NELSON: Thank you.

28 Dr. Kramer.

1 DR. KRAMER: I guess I'm mostly concerned  
2 about looking at the whole time trend of what's  
3 happened in terms of the frequency with which  
4 acetaminophen is present in such a variety of  
5 products that most patients -- I think somebody  
6 made the comment that, well, patients don't know  
7 what's in there, so -- you know, and yet we're  
8 really concerned about having to require data to  
9 take it out. But there wasn't very strong data in  
10 the first place for the peppering of acetaminophen  
11 through the whole shelf of OTC products.

12 I'm particularly concerned about  
13 unintentional use. And it seems to me that if  
14 people are taking a prescription product near the  
15 4 gram limit, and then they have an  
16 over-the-counter problem that they take a product  
17 for, that it's just to be expected that we'll  
18 exceed the toxic level.

19 DR. NELSON: Thank you.

20 Dr. Shrank.

21 DR. SHRANK: So if it's unintentional use  
22 that we're most concerned about, one observation  
23 is that if these products remain on the market, it  
24 looked to me like the label changes that were  
25 proposed weren't really sufficient to help  
26 patients better understand what the ingredients  
27 are.

28 It seemed that the ingredients -- the

1 listing of the ingredients was sort of in the same  
2 font and in the middle of the package. It wasn't  
3 really set aside, and there wasn't a lot of  
4 attention brought to those ingredients, and there  
5 wasn't any information about the dose of the  
6 over-the-counter ingredients that comprised the  
7 combination product. So my sense is that this is  
8 something that ought to be considered.

9 DR. NELSON: Dr. Lorenz.

10 DR. LORENZ: I wanted to speak as a  
11 primary care physician who is often struggling for  
12 solutions for patients who have low-level chronic  
13 pain. And, really, when I think about this  
14 category, I think about patients who are often  
15 self-managing who basically are avoiding  
16 medicalizing their problems and often trying to  
17 solve them in sort of creative ways.

18 And I just think we have to be cautious  
19 about eliminating an entire category of products  
20 that many people find useful. And while there may  
21 be specific problems, I'd like to address them  
22 specifically instead of as a class, and by all  
23 means want to help and encourage patients to be  
24 more active in the management of their own care,  
25 which this often facilitates.

26 DR. NELSON: It's Lewis Nelson. One  
27 thing that is a little bit interesting from an  
28 acute overdose perspective is that the mortality

1 associated with these combination products is much  
2 lower than it is with the acetaminophen-alone  
3 preparations, and that presumably has to do with  
4 the fact that, when you take them in excessive  
5 dose, you get sick from the other components that  
6 are in there, you know, your antihistamine or your  
7 whatever -- and you show up at the emergency  
8 department, whereas the people who take the  
9 acetaminophen preps alone, whether it's  
10 therapeutic or even intentional, may not even know  
11 that they're sick for the better part of a day or  
12 two.

13 And by the time they get to the  
14 hospital -- now, I'm not saying that that's a good  
15 thing in general, that we should put things --  
16 poisons in to make people sick. But the fact that  
17 it happens that way maybe masks in some level some  
18 of the problems associated with these products.

19 Again, the therapeutic misadventures that  
20 others are referring to are a different problem  
21 when you start combining different acetaminophen  
22 preparations.

23 Last comment from Dr. Totman.

24 DR. TOTMAN: I just wanted to clarify  
25 something that Dr. Shrank referred to, and that's  
26 the package labeling. In the added ingredient  
27 listing on the PDP there is still the ingredient  
28 listing on the active ingredients section of the

1 Drug Facts labeling that gives the dose of the  
2 drug at present.

3 DR. NELSON: Great. Thank you.

4 I think it's time to vote. And, again,  
5 the question we're voting on is, do you recommend  
6 eliminating nonprescription acetaminophen  
7 combination products?

8 Go ahead and vote now.

9 The voting results: Two said yes, high  
10 priority; 11 said yes; and 24 said no.

11 Would anybody like to explain their vote,  
12 when the votes come up? Or you can explain it  
13 anyway. Anybody have any comments?

14 Dr. Stergachis.

15 DR. STERGACHIS: Stergachis. Just a  
16 quick one. I think it's the way the question was  
17 worded on eliminating -- it's just so broad.

18 DR. NELSON: Agreed. And I think they  
19 got that message from us that there are many  
20 different products we're talking about, with a lot  
21 of different combinations, et cetera.

22 Yes, Dr. Farber.

23 DR. FARBER: Well, I think I probably  
24 alluded to it earlier, but my concern is that  
25 basically I'm not convinced of the efficacy of  
26 having acetaminophen in multiple drug preparations  
27 except in certain circumstances, and the FDA would  
28 have to look at those. But I think there is

1 clearly the potential for at least some harm.  
2 There are at least 10 percent of the patients who  
3 accidentally overdose due to taking multiple  
4 preparations. I think that's enough, in my mind,  
5 that the FDA should very seriously look at this.

6 DR. NELSON: Anybody else?

7 Dr. Omogui.

8 DR. OMOGUI: Yes. While I voted no to --  
9 I don't believe that all of these products should  
10 be eliminated. I still believe that listing the  
11 active ingredients under the ingredients list may  
12 not be enough, that there should be a broad  
13 display on the front of the package and says it  
14 contains acetaminophen. So that way people -- and  
15 don't just have to go and look at the active  
16 ingredient list. You can see it right in front.

17 Because it's still a problem in terms of  
18 taking multiple OTC combinations and consumers not  
19 knowing that they all contain acetaminophen. So I  
20 think the labeling may still need to be improved  
21 more than what we have right now.

22 DR. NELSON: Thank you.

23 Dr. Morrato.

24 DR. MORRATO: Yes. I'd like to add I  
25 interpreted it more as limit as opposed to  
26 eliminate, in interpreting that. And to some  
27 degree it relates to the confidence in which we  
28 think that the labeling changes -- and more



1           importantly, I think, the education program that's  
2           going to go, hopefully, with the labeling chang,  
3           in that, as we saw in our briefing materials,  
4           if -- you really did see a difference in knowledge  
5           and people's ability to know that it's in two of  
6           their different products -- that could change, you  
7           know, in terms of the need to use more -- stronger  
8           regulatory action.

9                     DR. NELSON:   Dr. Covington.

10                    DR. COVINGTON:  Yeah.  I voted no, but --  
11           and I'm not convinced that the benefits exceed the  
12           risks of the combination products, and I was  
13           thinking, I don't think I've ever taken one.  I  
14           try to figure out what I need, and then I go take  
15           that ingredient.

16                    But we really haven't been presented with  
17           data about the risks and benefits of combination  
18           ingredient products.  All we've been presented  
19           with is data about the risks and benefits of  
20           acetaminophen in those products.  And I think if  
21           we really wanted to look at the issue of the OTC  
22           combination products, that ought to be the subject  
23           of a separate -- because we don't have enough  
24           information to make that decision.

25                    DR. NELSON:  Thank you.

26                    Dr. Walker-Harding.

27                    DR. WALKER-HARDING:  Yes.  I wanted to  
28           say I voted yes because -- not because I think all

1       need to be eliminated, but I do think that it's  
2       pretty difficult to go to the drug store and try  
3       and figure what doesn't have acetaminophen, and it  
4       takes a while to -- looking on the back of boxes.  
5       And as a primary care provider, when you're  
6       working with people, it also takes a while to  
7       explain to them which they need and which they  
8       don't.

9               And I don't think there's a lot of  
10       evidence that acetaminophen is helpful to be in  
11       all of these products, and there should be some  
12       look at that.

13              DR. NELSON: Thank you.

14              Dr. Kramer.

15              DR. KRAMER: Yeah. I just wanted to  
16       explain my vote. I voted yes with high priority  
17       because I think this is, from my standpoint, a way  
18       to engineer in safety. If up to 40 percent of  
19       people don't need the ingredient, and yet they're  
20       getting it inadvertently -- and it's hard to find  
21       a product that doesn't have it -- it just seems  
22       obvious to me that that contributes to  
23       unintentional overdose.

24              What bothers me is when we say we need  
25       data to forbid this, but there was not extensive  
26       data required to create this situation. So I  
27       think it's a one-way thing where, you know, it's  
28       okay to add it because it's a marketing ploy; it

1 sounds like it's good because it's got a lot of  
2 ingredients, but in order to take it out, we've  
3 got to have much more data. And so it's just  
4 imbalanced, and I'm very concerned that that --  
5 we're asking too much to try to sit there at the  
6 shelf for a long time and read all these things  
7 and figure it out.

8 DR. NELSON: Dr. Griffin.

9 DR. GRIFFIN: Yeah. I would agree that  
10 we should consider the combinations together,  
11 because there are combinations of other  
12 analgesics, like aspirin and NSAIDs, and there  
13 might be substitution here, too, if we took  
14 acetaminophen out of all combinations. So -- and  
15 I think if we're labeling for acetaminophen, we  
16 should also be labeling for aspirin or  
17 aspirin-like products, which might be substituted.  
18 So I would agree that it's a potential problem,  
19 but I think just attacking the acetaminophen part  
20 is not sufficient.

21 DR. NELSON: Dr. Gellad.

22 DR. GELLAD: I'd just make the point that  
23 I think that there seems to be -- in some way,  
24 many people -- at least I feel that these products  
25 may be unnecessary, but whether or not they're  
26 leading to the harm that we're trying to look at,  
27 I'm not sure that there's enough evidence that  
28 they're really contributing to acetaminophen

1 overdose.

2           The other point I would make is I think  
3 this is going to be a case where we would see  
4 substitution without a doubt. Instead of  
5 acetaminophen, it's going to be Motrin. So I  
6 would just make that point as well.

7           DR. NELSON: Thank you. Any further  
8 comments?

9           FDA, any questions or issues?

10          DR. KWEDER: All the points that are made  
11 are the kind of things that we would hope would  
12 come out as part of this discussion. It's very  
13 helpful. Thank you.

14          DR. NELSON: Good. So we're going to  
15 move on to option 6. And option 6 is to limit the  
16 formulations of OTC liquids. And the vote, of  
17 course, is, do you recommend that one  
18 concentration of nonprescription acetaminophen  
19 liquid be available?

20          Yes, Dr. Cooper.

21          DR. COOPER: The guidance consideration  
22 to the general considerations sort of guide us to  
23 think about the potential for these questions to  
24 reduce the chance of liver injury, and we've  
25 discussed the fact that our focus is often on  
26 those inadvertent dosing issues. I think this  
27 provides a nice opportunity to take those things  
28 into account.

1                   From my review of the briefing materials,  
2                   the information yesterday, including the root  
3                   cause analysis, I think there's some element of  
4                   childhood overdose that is related to confusion  
5                   over the different formulations. In addition, in  
6                   my practice as a general pediatrician, I care for  
7                   families of infants, as well as young children,  
8                   and I find this to be a source of great confusion  
9                   for the families that I deal with that, when they  
10                  call and ask questions on the phone about how to  
11                  dose their child for fever control, there's often  
12                  a great amount of time and confusion spent trying  
13                  to sort out what formulation they have. And I'm  
14                  often concerned about the results of that.

15                 And I've not heard, in the information  
16                 that we've reviewed, any compelling reason for why  
17                 there should be these two formulations, and so I  
18                 think that, given the potential for risk and not a  
19                 lot of clear benefit, that this would be a  
20                 recommendation that I would be in favor of.

21                 DR. NELSON: Thank you.

22                 Dr. Benowitz.

23                 DR. BENOWITZ: The point I had is, like  
24                 Dr. Cooper, I would like to ask industry -- we've  
25                 heard what the downsides are of having two  
26                 different concentrations. What's the downside of  
27                 having one concentration?

28                 DR. KUFFNER: -- what the potential

1 benefit is of the lower -- or the more  
2 concentrated for the smaller children, so that you  
3 can give the smallest of children a lower volume,  
4 and that makes caregiver administration easier for  
5 the smallest of children.

6 DR. NELSON: But can I jump in and ask  
7 you, why can't you use that same concentration for  
8 larger kids?

9 DR. KUFFNER: You could use the -- you  
10 could use any of the concentrations for any -- any  
11 age range; it's just the more concentrated does  
12 make it easier for the smallest of kids.

13 The concern certainly, if you would only  
14 have the infants' concentration available, would  
15 be that, currently, carry-overs for older children  
16 are used to dosing in the larger volume, so the  
17 teaspoons are 5 mls, and certainly having just the  
18 more concentrated formulation on the market, that  
19 actually could create unintended consequences.

20 DR. NELSON: Right, assuming there's no,  
21 you know, easy transition from one to the other.  
22 But there's no larger child who's going to say,  
23 no, I need 15 mls or 10 mls; I'm not taking 3.

24 DR. KUFFNER: Right.

25 DR. NELSON: So if you give them the more  
26 concentrated -- I can see the other direction  
27 being an issue, of course.

28 DR. KUFFNER: Right.

1 DR. NELSON: Dr. Lorenz.

2 DR. LORENZ: So I'm unsure to what extent  
3 this would apply, but I think it's important to  
4 remember that it's not only children who might use  
5 a liquid formulation; there are adults who may  
6 have trouble swallowing pills. There are  
7 individuals who can't feed, who rely on the use of  
8 liquid formulations through G-tubes.

9 And so when we think about rationalizing  
10 the availability of particular doses and  
11 formulations, which I certainly would support, I  
12 think we want to keep in mind the diversity who  
13 might need to use a liquid product.

14 DR. NELSON: Thank you.

15 Dr. DeNisco.

16 DR. DeNISCO: I certainly respect the  
17 need to have different formulations, but I do  
18 know, having been on a pharmacy committee in a  
19 hospital, that when there are two medications of  
20 different concentrations, there's almost  
21 invariably a problem. And before those are  
22 allowed on, there has to be a very strong reason  
23 why there needs to be two concentrations.

24 Also, in the review material, I agree,  
25 from the direction a larger child is not going to  
26 say, gee, I need 15 mls; you're shorting me on my  
27 Tylenol. But they went -- in the review material  
28 we read, they -- I think it was some of the older

1 studies, when they went to neonatal intensive care  
2 units, which are certainly the smallest children,  
3 and they said, would the volumes -- if you had to  
4 use the less concentrated amounts, would these be  
5 a problem?

6 And they said, number one, we don't  
7 really use -- we follow the fevers; we don't  
8 really use antipyretics all that much, but if we  
9 did, it's still -- the volume is not so great that  
10 it would cause fluid overload. It's not anything  
11 that would be a problem in the neonatal setting,  
12 which is the most extreme example. So that's what  
13 we were provided with.

14 DR. KUFFNER: So I think that was one  
15 neonatal intensive care unit. When you do survey  
16 pediatricians across the board, the more  
17 concentrated infants' formulation is the preferred  
18 form that's recommended by pediatricians more than  
19 any other form for children under two years of  
20 age.

21 And I think here, as you debate this  
22 question, it really comes down to, what is the  
23 most impactful thing to do? And the most  
24 impactful thing is adding the dosing directions  
25 onto the label for children under two. And having  
26 read through all those different reports over a  
27 five-year period -- and there are relatively  
28 few -- and I've gone back and read every single



1 report that McNeil has within their database since  
2 the beginning of time where there's an issue -- it  
3 does become clear, if dosing directions were  
4 there, at least parents would have the  
5 opportunity, if a healthcare provider gave them  
6 the instructions, that they could double-check  
7 that dose on the package.

8 And so a measured approach at this time  
9 seems to be, put dosing directions on the package,  
10 and I think that will eliminate the vast majority  
11 of all of these overdoses in young children.

12 DR. NELSON: Thank you.

13 Dr. Wolfe.

14 DR. WOLFE: Going back to Dr. Kramer's  
15 remark many hours ago that as much as possible  
16 needs to be engineered, I think this is a good  
17 example of that. There is enough difference in  
18 understanding readability, transmission of  
19 information from doctors to patients that, as long  
20 as there are two different concentrations  
21 available, there will be problems.

22 I have not heard from anywhere here --  
23 Dr. Cooper is a practicing general pediatrician.  
24 Is there anyone else here who is a pediatrician or  
25 a pediatric nurse practitioner who thinks that  
26 there would be any downside of having just one  
27 concentration available?

28 DR. NELSON: Were you raising your hand

1 to agree or do you want to make a comment?

2 DR. WALKER-HARDING: No, to make a  
3 comment just to further --

4 DR. NELSON: Go ahead.

5 DR. WALKER-HARDING: I think it causes  
6 quite a bit of confusion to have two, and I think,  
7 if we did have the less than two recommendations,  
8 which appear to be further beyond what needs will  
9 take place, maybe the question of having two could  
10 be reconsidered. But until we have those kind of  
11 instructions, then we're going to continue to have  
12 the same problem of confusion.

13 DR. NELSON: Thank you.

14 Dr. DeNisco, you had another comment.

15 DR. DeNISCO: We've already heard that  
16 patients in general don't read labels, and I know  
17 parents are more concerned about their children  
18 than they are about themselves, but I'm still not  
19 that convinced that reading labels is the answer.

20 DR. NELSON: Dr. Krenzelok.

21 DR. KRENZELOK: Thank you. Krenzelok. I  
22 agree with Dr. Kuffner that education is extremely  
23 important in this area, and this is maybe the one  
24 place where education can make an impact, because  
25 parents are a lot more dedicated toward reading  
26 labels and trying to interpret them and give their  
27 children the right dose.

28 But my question goes to the agency,

1 really, is if we voted for a single formulation,  
2 what would you do in terms of concentration?  
3 Would you take the more concentrated dose? Would  
4 you have something in between?

5 Because I think that really, to me -- if  
6 it was the concentrated dose, I think I would be  
7 likely to vote for a single preparation, but if it  
8 was the dilute dose, I would be more likely to  
9 vote no on this one. So if you can shine some  
10 light on what you'd like to do.

11 DR. GANLEY: This is Charlie Ganley.  
12 It's not my decision, so I can only give you the  
13 perspective of the working group, as we were  
14 talking about this. And -- you know, I think the  
15 working group recommended to go down in age to six  
16 months, but we still had the concern that if  
17 there's a communication between a pediatrician or  
18 family practitioner and a parent to take a certain  
19 dose, that there still could be confusion, because  
20 there is already dosing on these concentrated  
21 drops.

22 And I've left some samples up there --  
23 it's in milliliters, and if the dose is given in  
24 teaspoons, and the parent doesn't read that box,  
25 they could still make that error. Okay. So just  
26 putting directions on the box that is in  
27 milliliters, yet the less concentrated suspensions  
28 are in teaspoons or milliliters, parents aren't

1 always going to make that connection.

2 So we still felt that there were going to  
3 be dosing errors. And I think we were leaning to  
4 a less concentrated solution so that, if there was  
5 a dosing error, it would be less likely to cause  
6 harm.

7 DR. NELSON: Dr. Day.

8 MS. DAY: One positive outcome of having  
9 one concentration at a weaker level is that there  
10 would be, initially, some problem in the  
11 transition, but eventually I think it would be a  
12 very good mnemonic for parents to know, the older  
13 the kid, the more you give. And that would be  
14 very helpful.

15 DR. NELSON: Dr. Chojkier.

16 DR. CHOJKIER: In regard to the last  
17 comment, the older the kid, the more you give, but  
18 in any concentration that would be applicable.  
19 What -- I think that I heard yesterday in some  
20 presentations that safety of administration and  
21 accuracy for administration was greatly enhanced  
22 by syringe systems and administration, so there  
23 are ways to implement this in a very safe manner  
24 that would not exceed the allowable dose. I mean,  
25 you can fill only so much of the syringe.

26 DR. NELSON: Thank you.

27 Dr. Vaida.

28 DR. VAIDA: A question was raised about

1 the adults and the strengths, and I guess I have a  
2 question. Is there an adult liquid? I know that  
3 it's available in the acute care setting, but is  
4 it over-the-counter? For FDA or --

5 DR. KUFFNER: There is an available  
6 over-the-counter adult liquid formulation.

7 DR. VAIDA: So then this is actually  
8 saying that would be eliminated?

9 DR. NELSON: Is that a nonprescription?  
10 What is the concentration of the compound? Is  
11 that 160 milligrams per 5 milliliters?

12 DR. KUFFNER: The adult strength is 1,000  
13 milligrams per 30 mls.

14 DR. NELSON: So -- and that's a  
15 nonprescription product as well?

16 DR. KUFFNER: That is over-the-counter.

17 DR. NELSON: But not available in  
18 pharmacies -- or it is?

19 DR. KUFFNER: It is available in  
20 pharmacies.

21 DR. NELSON: Oh, it is available. Okay.

22 That was, I think, what you were asking;  
23 is that not right, Dr. Vaida?

24 DR. VAIDA: Correct. Yes. Would that  
25 be -- I mean, if we voted yes for this, for one  
26 standard concentration, where I'm leaning -- I  
27 mean, does that eliminate that concentration,  
28 though? Is that what we're saying? Or would the

1 FDA do something with that?

2 DR. KWEDER: Our question is really  
3 mostly geared towards the formulations, the liquid  
4 formulations that are directed toward children.

5 DR. NELSON: Dr. Engle.

6 DR. ENGLE: Dr. Vaida just made my point  
7 about the adult formulations. My question -- I  
8 know it's a bad idea to change questions in the  
9 middle of a hearing like this, but can we  
10 specify -- because Dr. Krenzelok had my other  
11 concern; I'm more likely to vote for the  
12 concentrate form than the more dilute. And the  
13 way this is now, it's like a no-win because you're  
14 voting for something and you don't know what  
15 concentration you're voting for.

16 DR. NELSON: Would you like to explain --

17 DR. KWEDER: I think they can -- they can  
18 amend their answer; I think that's fine.

19 DR. ENGLE: So then qualify our answers,  
20 is what you're saying?

21 DR. KWEDER: Yes.

22 DR. NELSON: Dr. Farber, last comment.

23 DR. FARBER: I would unfortunately --  
24 sorry, but disagree with you. I think the less  
25 concentrated form is safer. If somebody gives  
26 more of the less concentrated form, they're less  
27 likely to overdose a child.

28 So I would -- if this is a situation in

1       which one is voting for the less concentrated  
2       form, I would basically vote for it; if it was  
3       more concentrated form, I would tend not to.

4               DR. NELSON: Well, we're leaving  
5       concentration out of it, it sounds like, and you  
6       can explain -- although you already have, so we  
7       don't have to do it again -- your answer after we  
8       vote.

9               Does anybody else have any comments?

10              QUESTION: So we're putting in the word  
11       "pediatric"?

12              DR. NELSON: Conceptually. I mean, I  
13       think that it's been explained that this is for  
14       pediatric doses, although we don't have to write  
15       it in.

16              You know, for what it's worth, I mean, in  
17       my practice at a poison center as well -- I mean,  
18       I've seen both overdoses or overuses in both  
19       directions, both the children's prep, you know,  
20       being inadvertently used to excess, and larger  
21       children taking the more concentrated form.

22              I don't really think that it's really  
23       safe to have two formulations out there, just  
24       because of the amount of confusion that it  
25       engenders. It's just -- it's confusing to people  
26       in healthcare, and I think it's confusing to  
27       people who are not healthcare savvy. So I do get  
28       very concerned about it, too.

1 DR. KWEDER: I'd like to just make a  
2 general comment that we could have asked, you  
3 know, four or five questions on this topic alone,  
4 and we chose not to because, as we started to  
5 write them out, it quickly became very confusing  
6 and started to feel like splitting hairs, and  
7 there are a lot of considerations that have to go  
8 into implementing anything that you vote on. And  
9 the conversation that you're having here helps us  
10 greatly in that way. So your comments are well  
11 stated.

12 DR. NELSON: Great. And now you'll get  
13 our vote.

14 If everybody is ready, we're going to  
15 vote on question number 6. Do you recommend that  
16 only one concentration of nonprescription  
17 acetaminophen liquid be available? And we are  
18 presumably talking about pediatrics, and we  
19 haven't specified the concentration at this point.

20 The voting results are in. Yes, high  
21 priority, 19; yes, 17; no, one.

22 I hate to single out this person.  
23 Dr. Krenzelok -- okay -- would you like to explain  
24 your thoughts?

25 DR. KRENZELOK: Well, the question was so  
26 ambiguous -- and it still was at the end -- and I  
27 said in my statement that if they were going to  
28 limit it to the less dilute form, that I would



1 vote no, and I would be very much in favor of the  
2 concentrated form, as a uniform dose all the way  
3 around, but the answer that I got was that it  
4 would probably lean toward the more dilute dose,  
5 so I was opposed to that.

6 DR. NELSON: Which brings up a good  
7 question, and I'll ask the FDA. Would you like,  
8 by maybe a show of hands, to see if people would  
9 prefer a more concentrated or dilute version?  
10 Would that be okay? Could we do that? I mean, we  
11 don't have to count, necessarily, but --

12 DR. GANLEY: If that's permitted under  
13 the rules of the advisory committee.

14 DR. NELSON: You have to tell me. I  
15 don't know. I was told by Elaine that we can do  
16 that, so -- does she know the rules? Because if  
17 you don't, we're in big trouble.

18 MS. FERGUSON: Let me just confirm with  
19 Karen, but I believe that it's fine to do.

20 Karen, I just want to confirm. The  
21 committee would like to be able to specify whether  
22 they would like to go with the more concentrated  
23 form or the more dilute form. Is that okay, for a  
24 show a hands?

25 DR. TEMPLETON-SOMERS: To clarify -- oh,  
26 a vote?

27 MS. FERGUSON: Well, it's not a vote.

28 DR. NELSON: Just a show of hands.

1 MS. FERGUSON: Just a show of hands.

2 DR. NELSON: No counting.

3 DR. TEMPLETON-SOMERS: The way you posed  
4 that, though, it sounded like we were choosing  
5 between the existing dilute dose and the  
6 concentrated --

7 DR. NELSON: No. I was --

8 DR. TEMPLETON-SOMERS: -- and the packet  
9 had a proposed intermediate dose, so it's  
10 getting --

11 DR. NELSON: Oh, okay.

12 DR. TEMPLETON-SOMERS: -- very confusing.

13 DR. NELSON: So maybe we shouldn't do  
14 this.

15 DR. TEMPLETON-SOMERS: This is the  
16 limitation. I think --

17 DR. NELSON: I was just going to try to  
18 mediate --

19 DR. TEMPLETON-SOMERS: -- the question is  
20 very clear.

21 DR. NELSON: Okay. So -- that's fine.  
22 We'll move on.

23 Dr. Omogui.

24 DR. OMOGUI: While I was among the  
25 majority that voted yes, I want to point out it's  
26 not just the concentration that can lead to errors  
27 in dosing. And one of the things in our handout  
28 was the issue of the measuring device, and that

1 leads to significant errors in dosing. And  
2 specifically the measuring cup.

3 I mean, I have had personal experience  
4 with that measuring cup with my daughter. I can  
5 hardly see the line, and it's been really  
6 difficult to get an accurate dose. And I believe  
7 that the other speakers here can comment on the  
8 discrepancies in dosing just in using those  
9 measuring cups, and that syringes may be much more  
10 accurate for this in terms of avoiding dosing  
11 errors and avoiding overdosage of these OTC  
12 formulations.

13 DR. NELSON: Thank you. It actually  
14 sounds like they're moving in that direction  
15 already, but that would be a good point for the  
16 last question, I think.

17 Yes, Dr. Shrank.

18 DR. SHRANK: Yeah, we can wait till  
19 question 11, but I would like to speak to that as  
20 well.

21 DR. NELSON: Yeah. I think, just to the  
22 order of business, it would be best if we held all  
23 these ancillary -- they're very good ideas,  
24 obviously, but they really just would move more,  
25 you know, simply if we put them at the end.

26 Okay. The next option is option 5b.  
27 We've moved on to prescription products --  
28 recognize -- so it's a slightly different set of

1 concerns. And option 5b is whether to eliminate  
2 the prescription acetaminophen combination  
3 products. And the vote will be, do you recommend  
4 eliminating the prescription acetaminophen  
5 combination products?

6 Comments? Dr. Omogui.

7 DR. OMOGUI: I believe that this is --  
8 that this doesn't present all the options that we  
9 need to vote on, and I would like the FDA to  
10 consider adding the option of reducing the  
11 strength of the acetaminophen in these  
12 opioid/acetaminophen combinations rather than just  
13 eliminating it completely.

14 Many of us are aware that eliminating it  
15 completely is really not going to be a valuable  
16 option because it's going to move hydrocodone from  
17 a schedule III to a schedule II. And there's no  
18 single hydrocodone product in existence today.

19 So we'd really like to have the other  
20 option, so we can have a vote on it to see how  
21 many people really prefer removing the  
22 high-strength opioid combinations -- that is, the  
23 750 and the 500 milligrams -- from the market.

24 DR. KWEDER: We're not going to add a new  
25 question. We're not allowed to add a new question  
26 to this. But if you look on the handout -- it was  
27 on page 2, the last bullet before you voted on  
28 question 1, which was -- question 1 was about --

1 and 2 were about the dosage in the OTC product.

2 The last bullet says that FDA will  
3 consider your responses to questions 1 and 2 when  
4 determining whether to reduce the current dosage  
5 strengths of acetaminophen in prescription  
6 products.

7 So that's exactly what we would take into  
8 account. And our question here is specifically,  
9 do you think that there should be no combination  
10 opiate and acetaminophen prescription products  
11 available?

12 And we would take the dosing that you've  
13 already discussed, or other comments you want to  
14 make about that into account. This is a yes or  
15 no: Should there be -- just like we asked you in  
16 general about the nonprescription products, do you  
17 think that there should be no combination  
18 acetaminophen/narcotic prescription?

19 DR. OMOGUI: The concern I have is that,  
20 in this kind of situation, I will vote no, that  
21 there should be the combination, but that will  
22 really not reflect the true -- my true opinion in  
23 that it's not as if I'm all gung ho about the  
24 combinations; I just want to have the dose  
25 reduced. And so -- I don't know. Maybe we can  
26 qualify the vote after the voting has --

27 DR. KWEDER: You certainly can qualify  
28 your vote. Or you could vote -- alternatively,

1       you could vote yes, provided that the amount were  
2       lowered.

3               We are not allowed to change the  
4       question.

5               DR. NELSON:   Dr. Benowitz.

6               DR. BENOWITZ:  I think this is really a  
7       critical question.  If we got rid of acetaminophen  
8       in these products, it would undoubtedly have a  
9       huge effect in terms of reducing unintentional  
10      toxicity.  So I think the benefit is really huge.

11              I've got two questions about -- or two  
12      concerns.  One is the logistical concern.  You  
13      know, I'm not sure why acetaminophen with  
14      hydrocodone is schedule II versus pure opiates  
15      being schedule III -- and that has huge  
16      implications for prescribing.

17              DR. KWEDER:  I can answer that.  That has  
18      to do with the Controlled Substances Act, and that  
19      is just a provision of the Controlled Substances  
20      Act that, in -- ingredient opiates are  
21      schedule II, but, in combination, they become  
22      schedule III.

23              We didn't write that act.  It's just the  
24      act.

25              DR. BENOWITZ:  So then the other -- so  
26      that's one concern that I have.  It's going to  
27      make it much more difficult for us to prescribe  
28      medications for pain.

1           The second thing is the concern about  
2 drug abuse because oxycodone, for example, when  
3 used alone, is a big abuse problem. And so I  
4 would be concerned that, if we force everyone into  
5 just pure narcotics, that there would be an abuse  
6 issue.

7           So there is no question that this would  
8 benefit reducing acetaminophen toxicity, but I'm  
9 not sure what the other side of it is. So it's a  
10 very tough question. If anyone has any comments  
11 about this --

12           DR. KWEDER: That's why we're asking.

13           DR. NELSON: Just for clarification, I  
14 mean, obviously what we decide here is -- or what  
15 we recommend here is -- its implications are going  
16 to be thought about in other venues. So it's not  
17 like, all of a sudden, hydrocodone floods the  
18 market. There are still other advisory committees  
19 and other people looking at how to better control  
20 the flow of hydrocodone, oxycodone and these other  
21 things.

22           DR. HERTZ: Can you clarify what you mean  
23 by that?

24           DR. NELSON: Yeah. In other words, I  
25 think his concern is that, if we suddenly delink  
26 the two and hydrocodone was available, all of a  
27 sudden people would start abusing hydrocodone  
28 extensively because it would now be available

1 alone and without acetaminophen, but we --

2 DR. HERTZ: No, it won't be available  
3 alone.

4 DR. NELSON: Right, because it's not  
5 available --

6 DR. HERTZ: Right.

7 DR. NELSON: -- is what you're saying.  
8 But, you know, his kind of link to OxyContin from  
9 oxycodone versus Percocet, right, and the abuse  
10 potential of the --

11 DR. HERTZ: Right.

12 DR. NELSON: So -- go ahead.

13 DR. HERTZ: So if the combination  
14 products were no longer available -- I mean, what  
15 we tried to bring out in the presentation and in  
16 the background package was you have to pick  
17 another alternative, and because -- not that we've  
18 ever said -- well, I guess I can't say what we've  
19 said no to in the past, but because there are not  
20 currently any approved single-agent hydrocodone  
21 products on the market, something else will have  
22 to be chosen.

23 I mean, it's very easy to see that  
24 unbundling would take care of the liver problem,  
25 but we're trying to get a sense of what the ripple  
26 effect will be in terms of other problems  
27 associated with replacement. So -- you're right.  
28 I mean, that's exactly the dilemma.



1           There are other efforts within the agency  
2           to address prescription opiate abuse. And we've  
3           had public meetings about risk evaluation and  
4           mitigation strategies. It's not entirely clear at  
5           this point, though -- right now we're not  
6           intending that necessarily to include  
7           immediate-release schedule II opioids. That was  
8           not our original intent. We don't have a final  
9           position on that in the sense that we're still  
10          taking into account the information and the  
11          feedback we got at recent public meetings.

12                 So to say we don't need to, today, worry  
13          about schedule II opioid use increasing because  
14          there will be a REMS, that's a very big jump, and  
15          I'm not sure that it's a safe thing to say yet.  
16          We don't know when the REMS will come into effect.  
17          And we don't know the extent of the products that  
18          will be covered.

19                 DR. NELSON: Okay. Thank you.

20                 Dr. Farber.

21                 DR. FARBER: So I think there are two  
22          things to think about in terms of this question.  
23          First, we're talking about the fact that half of  
24          all the unintentional overdoses in the country  
25          occur due to prescription types of acetaminophen  
26          products. So we're talking about, I guess, a  
27          quarter of all of the overdoses per year happening  
28          because of this.

1                   We -- let me give you an anecdote about  
2 something. We have an electronic progress  
3 record -- I will make the argument that I think  
4 it's a good thing to have it unbundled, and I  
5 would make the argument that it's a good thing for  
6 physicians to have to write a schedule II  
7 prescription, either with hydrocodone that is then  
8 NDA'd for schedule II on its own, or something  
9 else.

10                  The reason I say that is we have an  
11 electronic progress record. I have a patient come  
12 to me with pain of varying sorts, and I will  
13 initially write them an electronic prescription to  
14 the pharmacy for a hydrocodone/acetaminophen  
15 combination product for, let's say, a short term.  
16 And it's very easy for one of my colleagues, or  
17 myself, if I have forgotten, to go click, click,  
18 click, click, every time the patient calls and  
19 says, I need more, I need more, I need more.

20                  If I have to stop and write a separate  
21 schedule II prescription, which are not accepted  
22 electronically by pharmacies, I have to stop and  
23 think about it.

24                  I think it's actually a safer thing for  
25 multiple reasons for us to unbundle it.

26                  DR. NELSON: Dr. DeNisco.

27                  DR. DeNISCO: Being in addiction  
28 medicine, I certainly appreciate both sides of

1       this. Our national databases show that one in ten  
2       high school seniors is exposed to hydrocodone  
3       products, so that means that one in ten are being  
4       exposed to who knows how much acetaminophen, and  
5       certainly we do -- I am surprised that the amount  
6       of liver damage is not much greater, knowing the  
7       large doses, the large number of pills and number  
8       of grams of acetaminophen that many who are  
9       addicted to these substances take.

10               I just don't know why the numbers aren't  
11       higher. That's -- you know, thank God they're  
12       not.

13               So on the one hand, I think we're  
14       giving -- a tremendous amount of acetaminophen is  
15       getting out there. On the other hand, we do know  
16       that with the oxycodone products, when they're  
17       mixed, that you do not have the abuse that -- when  
18       you have to take a oxycodone product and mix it  
19       with aspirin or Tylenol or acetaminophen, it's a  
20       much bigger pill, and its abuse liability is much  
21       reduced.

22               And there's a number of things being  
23       worked on for abuse-resistant medication formulas,  
24       but those are still not quite on stage yet.

25               So I see this -- I do appreciate this is  
26       a real issue. However, I would agree that the --  
27       I would also point out that the amount of  
28       hydrocodone in this country is incredibly large,

1 and probably because it is relatively easy to  
2 prescribe. I'm not saying it's an excellent  
3 medication, needs to be out there, does a  
4 wonderful job, but we have to balance -- this is a  
5 case of balancing risks and benefits, and it's --  
6 that it can be called in I'm not sure is a patient  
7 benefit.

8 And while hydrocodone is no more abused  
9 than many other drugs, if you look at number -- if  
10 you calculate it in appropriate ways, nonetheless  
11 the amount of hydrocodone that is abused, because  
12 there is so much out there, is amazing.

13 So I would say we should do what's good  
14 medicine, and if good medicine dictates to you  
15 that you should prescribe an opiate and, to  
16 potentiate the opiate, perhaps a non-opioid  
17 analgesic, acetaminophen or aspirin or whatever  
18 you think, then that's what you should do  
19 medically. And if you have to write a  
20 prescription, then that's what you should do if  
21 that's what's the best medical thing to do.

22 I don't think that just looking at the  
23 convenience that it will rock the system -- and I  
24 agree it would rock the system, and a compromise  
25 would be to reduce the 750-milligram acetaminophen  
26 products all down. That would sort of be a  
27 compromise, but it wouldn't -- but if you think  
28 that's the answer, I would challenge you to say,

1 is that what is the best medicine?

2 So when you look at this, yes, it goes to  
3 this product. Other potential consequences of  
4 this change that should be anticipated -- I agree  
5 it would rock the medical system, but what's the  
6 best for the medical system?

7 DR. NELSON: Thank you.

8 Dr. Griffin.

9 DR. GRIFFIN: Yeah. I think this is a  
10 really tough problem, because this is clearly the  
11 biggest cause of the overdoses, but I guess I  
12 think that the use of these combination products  
13 has grown very quickly in the last five years, and  
14 it is amazing that we haven't seen even more  
15 toxicity, which makes me think that maybe some of  
16 the educational efforts have worked, because of  
17 the increasing use of these.

18 But I'm really worried about the  
19 substitution effects, that -- will people use  
20 plain narcotics? Will this really be an answer?  
21 And I think we need a broader answer to chronic  
22 pain because these drugs are being used  
23 extensively in the older population, and I'm not  
24 sure that practitioners feel like they have many  
25 other choices. And if the choice is plain  
26 narcotics, is that really going to be better? I'm  
27 not sure.

28 I think, if they stay on the market, we

1 have to find ways to make them safer, like  
2 limiting the acetaminophen, having better  
3 labeling, et cetera.

4 DR. NELSON: Dr. Lorenz.

5 DR. LORENZ: I would like to make the  
6 point that this is exactly why we need comparative  
7 effectiveness research. This is the kind of  
8 question where understanding the efficacy and the  
9 problems raised by alternative approaches to one  
10 of the most pervasive problems -- two of the most  
11 pervasive problems we suffer, both chronic pain as  
12 well as substance abuse, need to be examined  
13 empirically.

14 And while the question indeed is urgent  
15 to answer, so is the opportunity, and I guess I  
16 want to ask the question how our deliberations can  
17 inform that because I'm afraid that this sort of  
18 high-level attention unfortunately may be delinked  
19 from that process, but I think it underscores why  
20 it's important.

21 DR. NELSON: Dr. Chojkier.

22 DR. CHOJKIER: Just to emphasize a couple  
23 of points that have been made, I also agree that  
24 this is a huge problem. About 120 unintentional  
25 acute liver failures are due to this combination  
26 of hydrocodone/acetaminophen, and my view is that  
27 this should disappear. We can control it. This  
28 is more than all the other idiosyncratic liver

1 injuries that we see in the country in any given  
2 year. This is a huge problem.

3 There has never been a drug with this  
4 degree of mortality associated, and liver injury,  
5 in years and years, regarding the numbers in the  
6 country, relative percentages.

7 As Dr. Farber pointed out, we see a lot  
8 of abuses among veterans at the VA medical center,  
9 and teenagers at UCSD, that they have been  
10 prescribed the combination by one physician here,  
11 another physician there, and they shop around.  
12 And there is no way to control that. And this is  
13 increasing dramatically. We are not -- this  
14 facilitates drug addiction, and it would soon  
15 reach a point where we are going to be alarmed  
16 with -- the number of possibly  
17 acetaminophen-induced liver injuries may keep  
18 climbing.

19 I think it's a big high priority. I will  
20 vote it high priority, disassociate the two.

21 DR. NELSON: Dr. Heckbert.

22 DR. HECKBERT: Yes. Heckbert. Thank  
23 you. I think that this decision is really the  
24 most difficult and most important one that we're  
25 voting on today, and it is difficult because of  
26 all the problems with implementing decoupling of  
27 the narcotics from the acetaminophen in this case.

28 So I guess I would like to state that I

1 think that they should be decoupled, and that's  
2 the ideal solution, and that's what's best  
3 medicine. But I understand that the  
4 practicalities of doing that and getting the  
5 medical community and the regulatory community  
6 behind that is a tremendous burden.

7 If we, instead -- I think the fallback  
8 position, although I don't think it's optimal, is  
9 to reduce the amount of acetaminophen in these  
10 combination products. That's not optimal  
11 medicine, but it's a possibility.

12 DR. NELSON: Thank you.

13 Dr. Markman.

14 DR. MARKMAN: I would also like to throw  
15 my support behind Dr. Omogui's suggestion. I  
16 think the notion of reducing the amount of  
17 acetaminophen in these combinations is, at once,  
18 very pragmatic and will have probably an immediate  
19 effect on the problem which has brought us here  
20 today, or at least one of the most important ones  
21 regarding the mortality associated with these  
22 medications.

23 And I do think that, you know, the  
24 unintended consequences of taking the most  
25 commonly prescribed generic drug off the market in  
26 the United States without further study are  
27 unknown and would require just that -- further  
28 study -- before we could take such a step.



1                   And I think it would be a mistake to try  
2                   and address the complex problem of aberrant  
3                   drug-taking behavior with this drug and try and  
4                   sort of manage it through sort of a side door of  
5                   this one important problem which we're here  
6                   dealing with today, which is the hepatic mortality  
7                   associated with it.

8                   So I think that we need to deal with the  
9                   problems of misuse and abuse and diversion of this  
10                  drug and this class of drugs as a separate issue,  
11                  but perhaps take this pragmatic step which  
12                  Dr. Omogui has outlined today.

13                 DR. NELSON: Thank you. I mean, these  
14                 have all been excellent comments, and I'm not  
15                 stopping discussion, but I just want to point out  
16                 that it's 20 of 3:00. I'd like to end this  
17                 discussion of this agent by 3:00 before we take  
18                 our -- you know, a break at that time, and we  
19                 could move that one way or the other if we have  
20                 to. There are about 15 people left on the list to  
21                 talk which, if we limit it to one minute per  
22                 person, like we did last time, we can actually  
23                 accomplish that and still vote.

24                 What I'd ask you to do -- and I don't  
25                 want to keep people from saying something that's  
26                 fresh and important, but if you just -- if you're  
27                 going to reiterate something that's been said, do  
28                 it briefly, or don't do it. But it would

1           really -- Dr. Kweder.

2                   DR. KWEDER:   And I'd like to just clarify  
3           here that -- because you raised this question for  
4           us in the beginning, is there are other  
5           considerations related to the drug abuse problem  
6           and opiates that we are taking into account, and  
7           that's absolutely the case.  We are asking you, as  
8           a group, even though they absolutely impact each  
9           other, what your perspective is on the value for  
10          the hepatotoxicity of seeking to decouple these.

11                   And, of course, there are other -- you  
12          know, what is the value to that, considering the  
13          other implications of doing so?

14                   DR. NELSON:  All right.  So, with that,  
15          Dr. Covington.

16                   DR. COVINGTON:  I want to agree that  
17          the -- I'm a pain specialist and addictionologist,  
18          and the addiction business in America has become  
19          largely about iatrogenic addiction, so this is a  
20          huge issue that we're not going to address or  
21          solve any more than we are the role of opioids in  
22          chronic pain.  I think the real question that we  
23          have here is, does America need a reasonably  
24          potent schedule III opioid?  And physicians think  
25          so, and patients think so -- and you can prove  
26          that by the market share.

27                   So -- and there is no other that's really  
28          viable.  Percocet is schedule II, and codeine with

1 Tylenol is pretty weak. So we do need a  
2 schedule III narcotic available to us when we need  
3 to call something in. And the exigencies of our  
4 legislature are such that the only way you can do  
5 that is to mix Tylenol with it, or acetaminophen.

6 So I would propose that we do need to  
7 keep such a product available, and what we need to  
8 do is to absolutely minimize its toxicity by  
9 limiting the amount of acetaminophen in it to 100  
10 milligrams.

11 DR. KWEDER: The other schedule III that  
12 is available is Vicoprofen.

13 DR. COVINGTON: Yes.

14 DR. KWEDER: Which is hydrocodone with  
15 ibuprofen.

16 DR. NELSON: Thank you.

17 Dr. Krenzelok.

18 DR. KRENZELOK: I'll you give you back a  
19 minute, Lewis. Thank you. My questions have been  
20 answered.

21 DR. NELSON: Thank you.

22 Dr. Kerns.

23 DR. KERNS: Ditto.

24 DR. NELSON: Okay. Dr. Gellad.

25 DR. GELLAD: I actually want to bring up  
26 that point about the other schedule III because I  
27 think that's going to be a consequence, without a  
28 doubt. If you eliminate

1 hydrocodone/acetaminophen, the other easy one  
2 that's available is going to be this Vicoprofen,  
3 which is going to end up being a problem. So  
4 that's one point I would make.

5 The other point I would make is if we  
6 really think that acetaminophen and the narcotic  
7 are both necessary, and they're going to have to  
8 be prescribed separately, that's going to be a  
9 huge additional cost for patients. They're going  
10 to have to pay the copay for the narcotic, plus  
11 either an over-the-counter acetaminophen or  
12 prescription acetaminophen. So that's the other  
13 point I would make.

14 But it is -- since I've been talking  
15 quickly, and I still have plenty of time, it is --  
16 as a primary care doctor, it really is, as others  
17 have been saying, if you have someone who has  
18 pain, who can't tolerate NSAIDs, or tells you they  
19 can't tolerate NSAIDs -- you've tried  
20 non-pharmacological options -- it's really not a  
21 good option to have to go directly to a  
22 schedule II. I mean, I think that's the real  
23 problem. Even thought reducing -- even though  
24 there is a problem with hepatotoxicity.

25 So then -- lastly, I would just -- third  
26 or fourth or whatever -- support the idea of  
27 reducing the dose of acetaminophen in the current  
28 products.

1 DR. NELSON: Good. Thank you.

2 Dr. Wolfe.

3 DR. WOLFE: The presentation made in the  
4 public session yesterday afternoon by a liver  
5 expert -- I'm blocking on his name right now --  
6 was basically people get tolerant. In other  
7 words, they need higher and higher doses of the  
8 narcotic -- hydrocodone, whatever -- and,  
9 therefore, they drag up higher and higher doses of  
10 acetaminophen with it.

11 The suggestion about having a low,  
12 possibly almost homeopathic dose of acetaminophen  
13 just so that you can stay in schedule III, you  
14 know, says something about what's wrong with the  
15 Controlled Substances Act.

16 I remember when that was passed -- and  
17 it's not the only thing that's wrong with it --  
18 but I think that the uncoupling is incredibly  
19 important. Otherwise, as people become tolerant  
20 to it and need more and more doses, they get  
21 higher and higher amounts of acetaminophen.

22 So I would strongly support the  
23 uncoupling, and I think we can figure out ways of  
24 dealing with it.

25 DR. NELSON: Yes. Thank you.

26 Dr. Vaida.

27 DR. VAIDA: Yes. I just want to  
28 reiterate, when I walked in here, this was a

1 no-brainer to me, the importance. But when I  
2 heard all the prescribers talk about schedule III,  
3 there are -- I found several non-steroidal  
4 schedule III products out there. So -- there's  
5 not only that Vicoprofen. There's Ibudone and  
6 there's several of them right now that you can  
7 switch over to immediately with a non-steroidal.

8 So I just think it's important that -- I  
9 think these need to be unraveled, but as soon as I  
10 vote, I mean, I'm certainly going to add the  
11 caveat that this has to be carried over to  
12 non-steroidals because, from what I heard, people  
13 are going to switch immediately.

14 DR. NELSON: Dr. Eisenach.

15 DR. EISENACH: Our committee met a couple  
16 of months ago, looking at another product, and  
17 voted a majority to remove some combination  
18 products from the market. And in part it was  
19 because the combination didn't separate from  
20 acetaminophen by itself.

21 I think the fall-back position that we're  
22 talking about, about reducing the dose of  
23 acetaminophen -- if acetaminophen is the primary  
24 component of the analgesic, we may be losing  
25 efficacy as well.

26 I think absolutely these should be  
27 uncoupled. But my understanding of the FDA  
28 regulatory process is that you have to show that,

1 with the lower dose of acetaminophen, you still  
2 have a benefit of giving the acetaminophen, and  
3 that you can't just give a homeopathic dose.

4 DR. NELSON: Yes. Thank you.

5 Dr. Levine.

6 DR. LEVINE: Well, I say ditto to what  
7 Dr. Wolfe said, but I will say, in my long career,  
8 this is the best advantage we've ever had in  
9 preventing hepatotoxicity. And all the patients  
10 that get liver transplants that I see that can't  
11 get a transplant because a patient came in with  
12 acetaminophen toxicity -- and there are large  
13 numbers -- this is a major percent. Not only  
14 would people get better and there will be more  
15 transplants available to others; this is the first  
16 time I've ever seen that we'd have a major gain in  
17 hepatotoxicity, and as was mentioned before,  
18 there's only a minor number of patients, compared  
19 to acetaminophen, that we deal with in  
20 drug-induced liver injury. And it's going to stay  
21 that low-level amount.

22 But this is a major change, and I look  
23 forward to seeing it happen.

24 DR. NELSON: Dr. Omogui.

25 DR. OMOGUI: While still maintaining my  
26 position that we should keep the schedule III but  
27 reduce the acetaminophen, I would like to point  
28 out a couple of things.

1                    Delinking the acetaminophen completely  
2                    and moving to a schedule II does not decrease the  
3                    risk of addiction; it actually increases it.  
4                    You're going to exchange one problem for another  
5                    much bigger problem. Schedule II narcotics have  
6                    much more problems with abuse and diversion than  
7                    schedule IIIs.

8                    Also, changing hydrocodone/acetaminophen  
9                    combination to a hydrocodone/NSAID combination is  
10                   really also exchanging one problem for a much  
11                   bigger problem. There are a lot of patients who  
12                   can't handle NSAIDs, and NSAIDs have much more  
13                   side effects than the acetaminophen in terms of GI  
14                   bleeding, renal dysfunction, et cetera.

15                   I also address the issue of the Darvon,  
16                   the Darvocet, and acetaminophen. I was at the FDA  
17                   meeting when that was discussed. The issue of  
18                   delinking propoxyphene with acetaminophen was that  
19                   propoxyphene did not have any efficacy in any  
20                   study. This is completely different from  
21                   hydrocodone. Hydrocodone is an effective  
22                   analgesic, so we should not mix the two of them.

23                   So, again, the reason why we still need  
24                   to keep a degree of acetaminophen is that we're  
25                   going to have less issues of diversion of a pure  
26                   opioid, going to be able to keep this under  
27                   schedule III, and then we're going to solve the  
28                   problem, by reducing the acetaminophen from 750



1 milligrams to 325 -- I believe that would take  
2 care of a lot of the hepatotoxicity because, at  
3 750, at ten tablets, you're at 7.5 grams. At 325,  
4 at ten tablets, you're at 3.25 grams so -- which  
5 is well within the therapeutic dose. Thanks.

6 DR. NELSON: Okay. I'm going to make one  
7 last comment, if I can, and then I think we'll  
8 move on to the vote.

9 We've been talking a lot about the abuse  
10 potential, and of course the overdose potential of  
11 the opioids. I do think, though, that these  
12 combination products also set us up for these  
13 therapeutic misadventures and, you know,  
14 hepatotoxicity, independent of its abuse  
15 potential.

16 And I specifically bring up the issue  
17 of -- that I deal with almost daily, and many of  
18 you that work in hospitals do as well, which is  
19 medication reconciliation. And I know that -- I  
20 won't say daily, but not uncommonly some of the  
21 residents will come up to me for patients who are  
22 on chronic pain medications and not want to give  
23 them their prescription -- and they'll offer to  
24 give them some acetaminophen or something like  
25 that, not even recognizing perhaps that they're in  
26 the same product, that they're in the product,  
27 which concerns me because here we are, as medical  
28 personnel, doing medication reconciliation,

1 knowing we're looking at the patient's medication  
2 list and still prescribing them a drug that they  
3 shouldn't be on.

4 And now we're asking people -- and this  
5 goes for the over-the-counter products as well.  
6 We're asking people who aren't really medically  
7 trained, and may be educated to some extent about,  
8 you know, medications and, you know, other  
9 healthcare issues -- but we're asking them to  
10 understand and not take two medications at the  
11 same time that shouldn't be taken together.

12 So if we really don't do a very good  
13 job -- and we know there are a lot of limitations  
14 to medication reconciliation, and we see these  
15 things happen with all classes of drugs, it very  
16 much concerns me that if we keep them together,  
17 the same problem is going to continue on.

18 So this chronic therapeutic overdose is  
19 not going to go away.

20 Okay. With that, in order so that we can  
21 have a little discussion afterwards, although many  
22 of these comments have been made already, perhaps  
23 we could take a vote on question number 7: Do you  
24 recommend eliminating the prescription  
25 acetaminophen combination products?

26 Remember, vote -- yes, I highly recommend  
27 is A; recommend is B; and no is C.

28 All right. The voting results are yes,

1 high priority, 10; yes, 10; and no, 17.

2 Would any -- I'll ask if anybody has any  
3 comments to make. I know a lot of comments have  
4 been made already. Feel free, if you feel  
5 compelled to reiterate them, it we will have to  
6 limit discussion to some extent.

7 Dr. Kramer.

8 DR. KRAMER: I just want to say that I  
9 think this is the one place where we have the  
10 greatest opportunity to engineer in some safety,  
11 and I think it's concerning that the primary  
12 argument against it is convenience in terms of  
13 calling a schedule III, and really without a  
14 scientific rationale for the basis of schedule III  
15 in the first place, and we've just sort of  
16 accepted that.

17 I understand, I think from the background  
18 packet, that the FDA received an inquiry and  
19 advice from -- for advice on this issue about  
20 schedule -- revising the schedule. Am I wrong  
21 about that? Did I dream that? I thought it was  
22 in the packet somewhere.

23 But, anyway, I just want to say that we  
24 know that the natural history of chronic pain  
25 patients is escalation of the opioid dose. We  
26 know that -- we heard -- we're here because there  
27 are inadvertent overdoses that are fatal, and this  
28 is our one opportunity, really, to do something

1 that will have a big impact.

2 DR. NELSON: Thank you.

3 Dr. Raja.

4 DR. RAJA: As a pain practitioner in an  
5 academic institution, I'm very concerned about the  
6 consequences of eliminating prescription  
7 acetaminophen combinations. The majority of our  
8 referrals from primary care physicians are on  
9 patients who were given a schedule III drug, and  
10 if they need a schedule II or higher drugs, then  
11 they are referred to the pain clinic.

12 So the consequences of this could be,  
13 potentially, undertreatment of pain in a  
14 significant proportion of our population. And I  
15 don't think we have enough pain clinics to treat  
16 all patients who need schedule II or more  
17 important opioids.

18 DR. NELSON: Thank you.

19 Ms. Landis.

20 DR. LANDIS: Yes. I think this is a  
21 place where education plays into both physicians  
22 and pharmacists. Right now on the market these  
23 products are at the 4-gram limit if they are  
24 prescribed and used appropriately.

25 So I voted against uncoupling. I think  
26 that this is a place where education needs to be  
27 done, both for pharmacists, as gatekeepers, and  
28 physicians, who are prescribing. And if there's

1 patients that are moving up on the scale and need  
2 to move to something stronger, that's where the  
3 physician needs to move them out of the  
4 hydrocodone/APAP and into something that's going  
5 to be more appropriate for the patient. And we  
6 see that a lot in our practice of sometimes having  
7 to intervene when the patient says, it's not  
8 taking care of the pain.

9 So I think this is a place where  
10 education is very important. That's why I voted  
11 no.

12 DR. NELSON: Thank you.

13 Dr. Kerns.

14 DR. KERNS: Yes. I just want to make it  
15 clear that my no vote wasn't because of a concern  
16 about convenience, so I wanted to react to  
17 Dr. Kramer's statement. I think this is a very  
18 important tool in the provider's armamentarium in  
19 managing pain. And to make this shift without  
20 very clear understanding of the implications on  
21 the management of pain, a similarly important,  
22 maybe larger public health crisis in this country,  
23 would be a huge mistake.

24 DR. NELSON: Dr. Gellad.

25 DR. GELLAD: I also voted no for the  
26 reasons I mentioned before, and what others have  
27 mentioned. But I do agree also that this is point  
28 where education is really important. And we saw

1 from the data that many patients who are on  
2 Vicodin and these other combination products don't  
3 know that they're on acetaminophen products. And  
4 I always try to educate my patients.

5 But I would just make the point that this  
6 doesn't mean that we shouldn't do anything, but I  
7 agree that education is an important part for  
8 these meds.

9 DR. NELSON: Thank you.

10 Dr. Lorenz.

11 DR. LORENZ: I just want to make two  
12 points. First of all, I think it's important to  
13 stress the fact that the problems and challenges  
14 of prescribing two medications to many patients  
15 who are already on many medications are greater  
16 than two-fold when we split a prescription. And  
17 so I think -- there are many advantages to having  
18 simpler medication regimens in many of the  
19 patients that we be talking about implicitly.

20 Secondly, I think it's very important to  
21 recognize that the reason it's prescribed for pain  
22 and the problems associated with the prescription  
23 raise problems -- or raise the question not only  
24 of why patients escalate their dose, but why  
25 clinicians don't adequately manage pain, activate  
26 patients appropriately in self-management, and  
27 provide instruction and guidance that allows  
28 patients to take these medications both

1 effectively and safely.

2 The solution to the problem is not  
3 necessarily the right one. And so I share the  
4 concerns of clinicians who feel that this is  
5 removing an important option for patients and  
6 clinicians and potentially raising more serious  
7 problems. But I think those questions can be  
8 answered empirically, and I would no doubt embrace  
9 it if, in fact, we had any evidence that it was  
10 answering the problem for which we've elected this  
11 choice, or elected this as a group, without  
12 causing others. Thank you.

13 DR. NELSON: Thank you.

14 Dr. Omogui.

15 DR. OMOGUI: I voted no because I  
16 believe, as clinicians, the cure should not be  
17 worse than the disease, and taking off  
18 schedule III and moving it to schedule II would  
19 create far more problems and -- resulting in far  
20 more undertreatment of pain.

21 Nevertheless, I do encourage the FDA to  
22 move quickly to reduce the high-strength combo,  
23 because I think that's -- that's something the FDA  
24 can do a lot quicker than trying to move  
25 hydrocodone from schedule III to schedule II --  
26 the hydrocodone combinations.

27 So I believe that -- in terms of what  
28 we're here for today, in terms of the

1        hepatotoxicity, in terms of the multiple  
2        medications that patients have, taking off all  
3        those 750 milligrams and 500 milligrams  
4        combination with hydrocodone will do a lot. We  
5        don't have those combinations with oxycodone. So  
6        there is really no reason why we should have them  
7        with the hydrocodone. There's really no  
8        therapeutic efficacy, but rather we have a lot of  
9        risk. So the risk/benefit ratio really is very  
10       poor.

11                    And so I believe the FDA can move quickly  
12       on that. Thanks.

13                    DR. NELSON: Thank you.

14                    Dr. Farber.

15                    DR. FARBER: I agree that, basically,  
16       physicians need to have options for patients in  
17       terms of their pain management on an acute basis.  
18       Basically, the perfect option would be, beyond  
19       actually our committee or the FDA, and that is if  
20       hydrocodone alone were moved from a schedule II to  
21       a schedule III designation, but that would require  
22       something beyond all of this.

23                    But The other options that could be  
24       entertained would be -- that most physicians, I'm  
25       sure, would disagree with, would be limited doses,  
26       or something along those lines, so that patients  
27       couldn't keep on escalating.

28                    The problem is that most physicians, when



1       they see a patient with chronic pain, oftentimes  
2       will continue medications like hydrocodone with  
3       acetaminophen despite the fact that they need to  
4       move to something more chronic.

5               The -- I voted yes, and a high priority,  
6       because of the fact that we can save a lot of  
7       lives doing this.  If we're trying to save those  
8       lives of the people who have unintentional  
9       overdoses, this is the best way of doing it.

10              In the meantime, what we can do is  
11       provide pain by educating -- provide pain  
12       management by educating physicians about how to  
13       approach chronic pain and how to deal with  
14       patients who have this kind of chronic pain.  I  
15       think it's a far more -- better way of dealing  
16       with that than continuing to have a schedule III  
17       hydrocodone preparation that the physicians can  
18       sort of just call in without thinking about,  
19       really, what they're doing.

20              DR. NELSON:  It looks like that would be  
21       our last discussion point.  You guys did great.  
22       It's exactly 3:00.  We could take our break, and  
23       we'll be back at 3:15.  Thank you.

24              (A recess was taken.)

25              DR. NELSON:  Okay.  We are doing great.  
26       If everybody can find their seats, we can get  
27       started.

28              Okay.  We're still on prescription drugs,

1 and we're now on option 3 and option 4. It's a  
2 long option, so hopefully you could read through  
3 it, but basically it asks about unit-of-use  
4 packaging, or additional warning materials, and  
5 then it asks whether or not a boxed warning should  
6 be implemented, with or without the unit-of-use  
7 packaging.

8 So the vote that we're going to be asked  
9 to vote on -- and we'll do both questions together  
10 like we did with the first two questions, and  
11 we'll discuss them and then vote in sequence --  
12 is, if prescription acetaminophen combination  
13 products continue to be marketed, do you recommend  
14 that unit-of-use packages be required?

15 And then, do you recommend that FDA  
16 require a boxed warning for prescription  
17 acetaminophen combination products?

18 Anybody have any comments to lead us off?

19 Dr. Benowitz.

20 DR. BENOWITZ: Could I just from the FDA  
21 a clarification of what unit-of-use means.

22 DR. HERTZ: What we have in mind for the  
23 prescription products is that they not be  
24 repackaged at the pharmacy level. So it just  
25 means that they be dispensed in the packaging that  
26 we've already reviewed and looked at. It will  
27 have the formal container label.

28 The number of tablets, pills per bottle

1 is not something that we're necessarily interested  
2 in restricting or changing. So in this case  
3 unit-of-use is not about the number. We could  
4 have bottles of 30. We could have bottles of 300.  
5 That's not really the question. It's more about  
6 the package itself and what it looks like.

7 DR. BENOWITZ: Can I just follow up on  
8 that? If they're packaged in a bottle of 30, that  
9 means that, if you write a prescription, the  
10 patient has to get 30?

11 DR. HERTZ: Or bottles of ten. I mean,  
12 there can be multiple size options that the  
13 pharmacy can stock. We're not saying there can  
14 only be one. We're saying it can be flexible.

15 The point being sometimes unit-of-use  
16 packaging is intended to be connected to package  
17 size restrictions. What we had in mind for the  
18 prescription products was nothing to do with  
19 package size restrictions, but mostly to do with  
20 being able to ensure the labeling and, if you  
21 agree with the med guide, that the med guide be  
22 attached because that's a more reliable method of  
23 delivery.

24 DR. NELSON: Dr. Farber.

25 DR. FARBER: Well, it's interesting.  
26 I've just changed my mind. My concern initially  
27 was the difficulty for patients, in terms of  
28 getting a small number of pills, or that the pills

1 would be in blister packs or something like that,  
2 that they would find difficult to open.

3 My understanding now is your interest is  
4 just in the labeling part of this. And I think,  
5 given that fact, given the fact that we're only  
6 looking at the labeling issue, I think it's a good  
7 thing.

8 I don't know that it would be enough.  
9 We've talked about that. I think that any kind of  
10 education that we would be doing, any kind of  
11 labeling that we would be doing would not be  
12 enough, but certainly it would be something that  
13 we should do.

14 So I think both the unit-of-use packages  
15 with labeling that the FDA would mandate, as well  
16 as a boxed warning would always be good things.

17 DR. NELSON: Dr. Gellad.

18 DR. GELLAD: I agree conceptually with  
19 the idea of the unit-of-use to make the packaging  
20 more standardized, but I want to go back again to  
21 this number issue, because if I have someone on  
22 50 -- if I'm prescribing 50 pills of Percocet, and  
23 I want to slowly taper them down over the course  
24 of -- I don't know how much time -- does that  
25 prevent me from them doing 45 one week and 40 the  
26 next week?

27 In other words, is there really unlimited  
28 number -- I can prescribe 47 pills, or 25 pills,

1 or is it going to be limited in some way?

2 DR. HERTZ: We're trying to get away from  
3 large bulk packaging that gets repackaged in amber  
4 bottles -- we've already hear, you know, there's  
5 not a lot of interest, perhaps, by some parties in  
6 stating the full name of acetaminophen. We know  
7 there's difficulties with distribution of the med  
8 guides.

9 That's not to say a package can't be  
10 broken down, but the idea is to try and get the  
11 predominant method of dispensing these products to  
12 be standard and provide, to the extent possible,  
13 as much information for all involved.

14 So in terms of how you would prescribe  
15 it, I don't think that we would have a situation  
16 where you can't prescribe the number that you  
17 think is appropriate. That's not the intent.

18 DR. NELSON: Ms. --

19 DR. KWEDER: The prescription  
20 instructions would still be coming -- could still  
21 come from you.

22 DR. NELSON: Thank you.

23 Ms. Landis.

24 DR. LANDIS: I don't want to put any  
25 roadblocks in the way, but unit-of-use that's out  
26 there right now -- I can't say I have a single  
27 product that's on my shelf that's unit-of-use that  
28 has not been broken into, either because, A, the

1 patient could not afford the full unit -- say,  
2 with Imitrex for migraine -- or, B, the insurance  
3 limited the number of tablets the patient would  
4 have, or, C, the doctor has a very specific amount  
5 that he wants his patient to have.

6 And it's not just that product. Any of  
7 them that are the unit-of-use eventually get  
8 broken down to a smaller amount. You know, I  
9 think you have to ask the question, what about the  
10 patient that wants to have the trial -- I just  
11 want to try a few tablets before I get the whole  
12 package.

13 And I think you also have to take into  
14 context, we have physicians, pain physicians, who  
15 are very specific for a 28-day supply, because  
16 that's how they keep their patients regulated,  
17 versus maybe someone who might go to a general  
18 practitioner, they may be looking at a 30-day  
19 supply because that's what the instructions pays  
20 for the patient, or it's a 90-day.

21 So I think you really have to look at it  
22 carefully. I'm not saying it can't be done, but a  
23 lot of times these good intentions just don't turn  
24 out that way.

25 DR. NELSON: Dr. Morrato.

26 DR. MORRATO: I had a follow-up point on  
27 clarifying. So if I'm understanding correctly,  
28 going to a standardized unit-of-use packaging is

1 as a vehicle to deliver a medication guide to  
2 everyone. Ideally, you would like the medication  
3 guide to everyone, but you're feeling that,  
4 without a unit-of-use packaging, that the  
5 likelihood of everyone getting it would be  
6 diminished?

7 DR. HERTZ: I think we have pretty good  
8 data that shows that the delivery of med guides is  
9 only a fraction of what we would hope.

10 DR. MORRATO: Okay. So I have concerns,  
11 then, that we're doing a lot of effort in order to  
12 try and do a better job of communicating a  
13 labeling and -- information there.

14 Was there any consideration of the  
15 auxiliary labeling and ability to influence that  
16 in terms of what's actually on the bottle in terms  
17 of, you know that's what a person carries with  
18 them long term after they've thrown out whatever  
19 they've gotten from the pharmacy?

20 DR. HERTZ: Well -- so we don't have  
21 direct authority to alter what's done in the  
22 pharmacy. And we've asked that they spell out  
23 acetaminophen; it wasn't very effective. We  
24 requested of the state boards of pharmacy in the  
25 past.

26 In terms of the bottle that would be  
27 delivered in unit-of-use, at the very least, it  
28 would have clear identification of what the

1 product is, and sometimes we can put a little bit  
2 of additional information, depending on the size  
3 of the bottle, in terms of warnings, key important  
4 messages.

5 DR. MORRATO: Right. And I'll defer to  
6 my pharmacy colleagues, but what I'm talking about  
7 is those little stickers you get on the side that  
8 says, Don't go out in the sun, don't drink this,  
9 which -- I don't know if you have data as to how  
10 effective they are relatively speaking --

11 DR. KWEDER: That's pharmacy practice.  
12 It's regulated by the states.

13 DR. MORRATO: And is that influenced, if  
14 it's a boxed warning, on the likelihood of that  
15 information -- if you had a boxed warning, being  
16 more likely to be on in the pharmacy? Does anyone  
17 know?

18 DR. HERTZ: There's -- no. The boxed  
19 warning is not -- is drug-specific information.  
20 Unless it happens to overlap with "take with  
21 food," "do not go out" -- but if there's anything  
22 in there that's not part of that standard  
23 practice, it doesn't usually show up in a label.

24 DR. MORRATO: Okay. Thank you.

25 DR. NELSON: Thank you.

26 Dr. Shrank.

27 DR. SHRANK: I just wanted to lower  
28 everyone's expectations of the effectiveness of a



1 medication guide, especially in this setting where  
2 patients are getting, in addition, a consumer  
3 medication information leaflet and, you know,  
4 everything that comes on the container or the  
5 package. I would just sort of urge folks to  
6 have -- so our research suggests that patients, in  
7 addition to rarely getting medication guides, they  
8 rarely read medication guides, and they rarely  
9 understand the medication guides.

10 So I don't think that should be a strong  
11 motivation for this question.

12 DR. HERTZ: But just to keep people in --  
13 we have a separate question about medication  
14 guides. This isn't the only point. It's also to  
15 make sure that the label on the bottle itself is  
16 more standardized.

17 DR. NELSON: Okay. Thank you.

18 Dr. Wolfe.

19 DR. WOLFE: My question, as sort of the  
20 subtext of question 9 -- you're saying that if we  
21 voted yes on question 9, boxed warning, that then,  
22 therefore, there would be medication guides for  
23 all these acetaminophen combination products, or  
24 no?

25 DR. HERTZ: We have the opportunity to  
26 explore them each independently, so the boxed  
27 warning is one item, the med guide is another  
28 item, and the unit-of-use is a third.

1 DR. WOLFE: Okay. But at least it would  
2 set up the situation where you would more easily  
3 be able to get a medication guide out, if you  
4 wanted to do one.

5 DR. HERTZ: (Nodding head.)

6 DR. WOLFE: Okay.

7 DR. NELSON: Dr. Chojkier.

8 DR. CHOJKIER: It has been answered  
9 already. Thank you.

10 DR. NELSON: Dr. Pollock.

11 DR. POLLOCK: I just have an additional  
12 question about clarification. This would also  
13 apply to, for instance, my dentist's office --  
14 where he repackages and sends me home with  
15 Vicodin, it would now have a label, because it  
16 does not previously, that states that it has  
17 acetaminophen in it; is that correct?

18 (No response.)

19 DR. NELSON: Dr. Stergachis.

20 DR. STERGACHIS: I think my question was  
21 answered with regard to med guides, so I'll defer.

22 DR. NELSON: Dr. Day.

23 MS. DAY: Comment about med guides.  
24 We've done research on them also, and there are  
25 difficulties, but we found people do get the main  
26 messages. So that's one point.

27 And about auxiliary labels, that does  
28 happen on a pharmacy basis. And it used to be you

1       could get the same medication multiple times and  
2       get different labels on it -- Take with food,  
3       Don't go out in the sun -- different ones at  
4       different times.

5               However, the vendors that put out the  
6       labels that go on the bottles and all of the  
7       information -- the CMI, the consumer medical  
8       information, they now in many places come out all  
9       on one big sheet. And so the pharmacist can tear  
10      off the information for the patient, and all of  
11      those appropriate auxiliary labels are there as  
12      well.

13             I don't know what percentage of  
14      pharmacies have gone to that, but that part of it  
15      has gotten better.

16             So both on the med guides and the  
17      auxiliary labels, both have gotten better than  
18      they used to be.

19             DR. NELSON: Dr. Morrato.

20             DR. MORRATO: I just wanted to clarify,  
21      so I'm understanding correctly, if you have a  
22      unit-of-use dose, but the pharmacist needs to  
23      break into it for that patient, the patient is  
24      still going home with a bottle that's -- the amber  
25      bottle, et cetera. They're not necessarily  
26      getting that package that was broken into. Is  
27      that correct?

28             DR. NELSON: Do you have an answer?

1 DR. LANDIS: Yes. There's nothing out  
2 there that restricts pharmacists from breaking  
3 those unit-of-use packages. And so if that is the  
4 request of the physician or, more importantly, the  
5 insurance now, because, if they limit what they  
6 have, that's all the patient gets, period -- we  
7 have to take care of the patient. And so --  
8 that's a priority. And so it does go into, you  
9 know, one of the -- just a regular standardized  
10 bottle.

11 DR. NELSON: I'm sorry. Was your  
12 question whether they give them the actual bottle  
13 that original came in?

14 DR. MORRATO: Right. So if I'm  
15 understanding, the value of the unit-of-use is  
16 that everyone gets -- just like when you go to the  
17 over-the-counter, everyone has that same package,  
18 that same warning, that same communication, and  
19 that's wonderful.

20 But if -- I don't know the percentage in  
21 this case, but if you're getting it broken into,  
22 that piece of material stays in the pharmacy --  
23 that's what I'm trying to clarify. And the  
24 patient is still going home with a bottle that  
25 doesn't have that special message on it anymore.

26 DR. LANDIS: That could be solved. I  
27 mean, if they were saying unit-of-use, but they  
28 can be broken into, you could have multiple copies

1 of the information with that product so that that  
2 could be broken into, and those individual  
3 information being given out to the patient, so...

4 DR. NELSON: But -- I'm sorry. If you  
5 have a unit-of-use -- you know, if you have a  
6 bottle of pills that contains 30 pills, and the  
7 doctor wants to give you 28 pills, it would seem  
8 obvious to me that they just take two pills out  
9 and give you the bottle. Is that not what we're  
10 talking about?

11 DR. LANDIS: What are you going to do  
12 with those two pills?

13 DR. NELSON: I mean, I can't see how it  
14 would be any different than the other way. I  
15 mean, those two pills would have to be wasted in  
16 some appropriate way or whatever. I don't know  
17 what they do in pharmacy.

18 DR. LANDIS: I can't do that in a  
19 pharmacy. I have to keep that medication in its  
20 original bottle with the expiration date and the  
21 code, in case there's any type of problem with it.  
22 So I can't just toss those pills away. That has  
23 to stay in that bottle.

24 So when you break into it, you're  
25 basically creating a new product for that. You  
26 still have all that information that's necessary  
27 as though it was any other prescription. The only  
28 difference may be is that -- you know, whether

1       it's little individual pills that are wrapped up,  
2       or they're loose ones; they will go in the bottle.  
3       It goes to the patient. It would be the same as  
4       if you had any other prescription out there.

5               But is a problem that we have.

6               DR. HERTZ: That's not to say there can't  
7       be 28-count pills, and then patients then get an  
8       additional two. I mean, I think the idea would be  
9       to try and do this wisely to maximize the  
10      likelihood of somebody requiring these products to  
11      get the information.

12              And Dr. Ganley reminds me that we  
13      actually have examples of labels where warning  
14      information was added to the unit-of-use  
15      packaging, so it's been done and could easily be  
16      done for this.

17              DR. NELSON: Yes, Dr. Stergachis.

18              DR. STERGACHIS: Just a quick follow-up.  
19      One practice that might reduce the effectiveness  
20      of unit-of-use, if the intent is to standardize  
21      the information on the product itself, is that  
22      prescriptions need to be dispensed with a label,  
23      and oftentimes the label goes right over whatever  
24      information is contained on that unit-of-use  
25      package. So I think we need to be thinking about  
26      some of the practicalities if we're trying to  
27      address the very important issue of labeling,  
28      having heard it's a weak intervention to begin

1 with, and secondly, the practical aspects might  
2 include that information just simply being covered  
3 by a state board of pharmacy mandated label.

4 DR. NELSON: But do we understand that  
5 the FDA doesn't have control over that? That's  
6 the state board of pharmacy that we heard about  
7 earlier today.

8 Yes. Go ahead.

9 DR. GANLEY: This is Charlie Ganley. I  
10 think the concept here is that there are a lot of  
11 stakeholders that have to buy into this, so if  
12 these products would remain available, they have  
13 to try to adapt to how -- if there were going to  
14 be unit-of-use packages, physicians would have to  
15 adapt, pharmacists would have to adapt to  
16 availability.

17 Now, there are probably close to 200  
18 abbreviated new drug applications for these  
19 opioid/acetaminophen combinations -- the generic  
20 ones. So our feeling, you know, when we were  
21 talking about this in the working group, was that  
22 companies will come up with ways to create  
23 products that will give a lot of discretion to  
24 pharmacists and physicians when they're  
25 prescribing this, but I think this gets back to  
26 the point that there has to be some part that the  
27 stakeholders, including physicians and pharmacists  
28 play in this.

1           If they're going to continue the same  
2 processes that are in place, this problem is not  
3 going to be solved.

4           So they're going to have to adapt to  
5 this. There has to be a change. It cannot just  
6 be a regulatory change.

7           DR. NELSON: Thank you. Fair enough.

8           Any other comments before -- Dr. Shrank.

9           DR. SHRANK: So one of the good things  
10 about unit-of-dose [sic] packaging is that it  
11 would create some sort of standardization. But  
12 it's hard -- we have to recognize that this is a  
13 medication that's being taken along with a number  
14 of other medications, and there's huge variability  
15 in the kinds of labels and presentation of all the  
16 medications that they're getting. And this will  
17 be another source of difference, another --  
18 incrementally, an increase in the variability of  
19 the presentation of the information that they're  
20 getting across all of their medications.

21           So it seems like -- you know, I could see  
22 a benefit, but there's also risks involved as  
23 well.

24           DR. NELSON: Yeah. And, you know, I  
25 actually think you have to differentiate the  
26 people who are getting a dose of this medication  
27 for the first time, and probably won't see it  
28 again for years, versus those who get it



1 recurrently, in terms of the amount of information  
2 that they're going to get out of the label and the  
3 medication guide that we provide for them.

4 Because obviously, I would imagine -- maybe it's  
5 not obvious -- that the people who get this  
6 recurrently are not going to read the medication  
7 guide and the label each time they get the  
8 medication. There's going to be a certain level  
9 of understanding of expectation.

10 So for those that get it for once in a  
11 while, maybe there would be some real benefit.

12 If there's -- Dr. Griffin.

13 DR. GRIFFIN: Yeah. It just seems like  
14 if these drugs are going to stay on the market --  
15 and clearly the committee was split -- that  
16 patients need more information, and maybe the  
17 label isn't the best way. But it seems like  
18 people don't know they're taking acetaminophen,  
19 and they don't know how many pills it's safe it  
20 take. And it seems like that should be mandated  
21 somehow, that people should know that they're  
22 taking acetaminophen and that X number of pills is  
23 the maximum dose.

24 And I'm not sure if anybody has any other  
25 ideas of how to get that information to the  
26 patient, because the doctors aren't telling them  
27 that, and the pharmacists aren't telling them  
28 that.

1           So -- I mean, it sounds like this is a  
2 weak solution to that problem, but I'm not sure  
3 that there's any another.

4           DR. NELSON: Dr. Chojkier.

5           DR. CHOJKIER: A question for the FDA.  
6 Isn't one of the potential solutions the  
7 incorporation of a black box, or any color box,  
8 that would be mandated, so then a state group  
9 would have to follow the recommendation of the  
10 FDA; isn't that correct?

11          DR. HERTZ: A boxed warning goes on the  
12 package insert. Package inserts are meant for the  
13 prescriber, not the patient. So the boxed warning  
14 and the delivery of the med guide are sort of  
15 separate. The boxed warning is an attempt, on the  
16 package insert, to sort of reawaken the physician  
17 to the important safety warnings.

18          There is going to be information in the  
19 boxed warning that will be of high priority in the  
20 medication guide -- so there's a relationship in  
21 terms of the material. But the boxed warning is  
22 in the package insert, not on any of the labels.

23          DR. NELSON: Dr. Benowitz.

24          DR. BENOWITZ: Just a follow-up on the  
25 black box warning. It seems like a very logical  
26 thing to do. Is there any downside to it?

27          DR. HERTZ: None that we can describe.

28          DR. NELSON: Okay. Last comment.

1 Dr. Stergachis.

2 DR. STERGACHIS: If we're -- Stergachis.  
3 If we're talking about black box warnings, could  
4 the FDA clarify whether that is associated with  
5 any restrictions on things like advertising?

6 DR. HERTZ: The information in a boxed  
7 warning must be presented in drug advertisements.

8 DR. NELSON: Any other pressing comments  
9 or questions?

10 Okay. Then it's time to vote. We'll  
11 vote on question number 8, and then we'll come  
12 back to question number 9.

13 Question 8: If prescription  
14 acetaminophen combination products continue to be  
15 on the market, do you recommend that unit-of-use  
16 packages be required?

17 The voting results: Yes, high priority,  
18 five; yes, 22; no, 10.

19 As per Dr. Wolfe's recommendation the  
20 first time, what we'll do is we'll go and vote on  
21 question number 9, then come back for the  
22 discussion.

23 Do you recommend that FDA require a boxed  
24 warning for prescription acetaminophen combination  
25 products?

26 Question number 9, voting results: Yes,  
27 high priority, 25; yes, 11; no, one.

28 I guess I'll open it up to comments,

1 particularly from Dr. Griffin, if she's  
2 interested.

3 DR. GRIFFIN: Well, we didn't really talk  
4 about this much, but, I mean, I think black box  
5 warnings, as FDA said, are directed toward  
6 prescribers, and unless there's a lot of  
7 education -- or other things that go with them --  
8 by themselves they don't do much.

9 And then I think -- we didn't really  
10 discuss the advertising part, about putting a  
11 black box warning on acetaminophen, you know, just  
12 a safe drug, versus not having it on other drugs.  
13 So I'm not sure that it would do much except maybe  
14 steer people away from acetaminophen, but not  
15 really address the problem of these combination  
16 use that we have.

17 DR. NELSON: Any other comments?

18 Dr. Day.

19 MS. DAY: I'd like to disagree with the  
20 last comment. Having studied comprehension of  
21 boxed warnings, I know what their drawbacks are,  
22 and they can be communicated better, more better  
23 than at present.

24 However, there is a very nice side effect  
25 of voting this in, and that is that the press,  
26 when they write up the results of these meetings,  
27 often say something like, and the boxed warning is  
28 the highest warning that the FDA can give -- is

1 generally the way they say it.

2 And I think there will then be a  
3 trickle-down effect throughout all of the  
4 prescription and nonprescription options that we  
5 talked about today. It will just alert people  
6 that maybe acetaminophen needs to be thought about  
7 a little bit more.

8 DR. NELSON: Dr. Morrato.

9 DR. MORRATO: I did vote yes on the  
10 unit-of-use packaging, but I guess I just would  
11 like -- hope that the FDA -- in working it with  
12 200 manufacturers, possibly, that are doing the  
13 packaging, each coming up with creative solutions,  
14 that there's some sense of standardization at  
15 least in how the unit of packaging is done across  
16 the products.

17 DR. NELSON: Dr. Covington.

18 DR. COVINGTON: Yeah, I just have a  
19 question. I was surprised to read, in our  
20 briefing materials, that while advertisements to  
21 physicians are required to list warnings,  
22 advertisements to patients of OTC products are  
23 not, which I found absolutely astounding, since  
24 presumably we're educated and they're not.

25 There's no place in this. Do we need to  
26 discuss that? Is that sort of like the law of  
27 gravity; it's immutable and we just live with it?

28 DR. NELSON: I think they are regulated

1 by different agencies, but perhaps FDA can answer.

2 DR. GANLEY: This is Charlie Ganley. As  
3 mentioned in one of the talks, the FTC regulates  
4 that, but you're certainly welcome to add any  
5 comments to this record if you think that should  
6 be different.

7 DR. COVINGTON: Yes, I think it should be  
8 different.

9 DR. NELSON: That's a comments. Good.

10 Any other comments or explanations,  
11 clarifications?

12 Okay. Move on to question number 10. So  
13 question 10 -- this is a special multiple-choice  
14 question, with more choices than there are buttons  
15 on the microphones. In order to preserve the  
16 simultaneous voting system, this vote will be done  
17 on paper ballots, which we be tabulated during our  
18 next discussion, I think, rather than a break --  
19 it's not really a good time for a break -- and the  
20 results displayed when we return from when we end  
21 our discussion, or when we return from the break.

22 Each member will find in their folder a  
23 green paper ballot with your name on it. Before  
24 we start the vote, of course, we'd like to have a  
25 discussion about some of the issues surrounding  
26 question number 10. So basically what we're going  
27 to do here is rank -- prioritize the options as  
28 which you feel is the most important one.

1                   So options related to both prescription  
2                   and over-the-counter products containing  
3                   acetaminophen have been discussed. You have  
4                   already indicated whether you condition each  
5                   individual option a high priority. To further  
6                   clarify how FDA should focus its resources to  
7                   decrease the public health burden of acetaminophen  
8                   liver toxicity, indicate the single option,  
9                   including both nonprescription and prescription  
10                  options, which you recommend that FDA consider its  
11                  highest priority. If you do not recommend the FDA  
12                  implement any of the proposed options, please  
13                  indicate this on the ballot provided.

14                 So you see the options there listed out.  
15                 Would anybody like to make a comment?

16                 Dr. Kramer.

17                 DR. KRAMER: I'm just curious why the FDA  
18                 wouldn't want people to just rank a numerical  
19                 order of all of the options. You could still  
20                 choose number 1 and tabulate that, but you'd have  
21                 more information than you would by just choosing  
22                 one.

23                 DR. KWEDER: Judy, I'll respond to that.  
24                 We did consider it. It would take us probably --  
25                 we figured out how long it would take us to  
26                 tabulate all of that, and it would be several  
27                 hours.

28                 And also we do believe that -- you know,

1 I can tell you that we have -- so far, we have had  
2 73 votes as high priority. There are more -- so  
3 clearly people are voting more than once. We have  
4 records of who has voted as a high priority on  
5 what items. So we have a lot of that information  
6 already that we can take back and take into  
7 account.

8 But we wanted you to really go through  
9 the exercise of thinking about this, and if you  
10 could -- because we can't do all of these right  
11 now; we simply can't. So this is really, where do  
12 we go first?

13 DR. NELSON: Any other discussion items  
14 at this point, before we rank?

15 Dr. Benowitz.

16 DR. BENOWITZ: Two things. Are we  
17 supposed to rank one in each category of  
18 nonprescription and prescription, or just one for  
19 all of them?

20 DR. KWEDER: One for all of them.

21 DR. BENOWITZ: And if we have something  
22 else that's not on the list, where does that go?

23 DR. KWEDER: That's part of the  
24 discussion for question 11.

25 You know, please keep in mind that for  
26 this kind of a committee, really -- you know,  
27 while we go through the exercise of voting and try  
28 to make you commit yourself one way or another,



1 really, for us, your discussion is as or more  
2 important than the vote itself, particularly when  
3 we have a circumstance here where most of the  
4 votes, if you just divide them by yes/no, are  
5 relatively -- they're all over.

6 And I would just reassure you that, in  
7 many respects, this is not a surprise to us. It's  
8 exactly what we experience ourselves in talking  
9 about that -- you probably got that flavor from  
10 reading the working group report. And this is a  
11 very -- this is really a very difficult set of  
12 options. It's a very difficult circumstance. We  
13 have presented the data that are available. We  
14 aren't withholding anything from you.

15 But this is where we find ourselves, and  
16 we need your help.

17 DR. NELSON: Okay. I was told it would  
18 take them 13 from the time they walk out the door  
19 to tabulate the votes. Is that right?

20 DR. KWEDER: (Nodding head.)

21 DR. NELSON: That's what Elaine told me.  
22 So we have 13 minutes --

23 DR. KWEDER: If they're good.

24 DR. NELSON: -- or more to discuss  
25 question number 11. I'm sure we could do better  
26 than 13 minutes. We have a lot on the list  
27 already.

28 What other options should FDA consider

1       that have not been discussed in the options  
2       already provided?

3               Just quickly, does everybody have a  
4       comment on this? I mean, should we just go around  
5       the table and let everybody just comment? That  
6       doesn't mean you should comment for ten minutes.  
7       If you don't have anything to say, please pass.  
8       And if you feel like you have something to add,  
9       please do. We'll probably start becoming  
10      repetitive at some point, so try to limit what you  
11      have to offer.

12              We'll start with Dr. Totman at the end.

13              DR. TOTMAN: Well, definitely we want to  
14      encourage the educational program that's been  
15      mentioned by both the CHPA and McNeil and the  
16      other manufacturers.

17              DR. NELSON: You might just say your  
18      name, perhaps, before you --

19              DR. MCLESKEY: McLeskey, pass.

20              DR. DeNISCO: DeNisco, pass.

21              DR. GELLAD: Gellad. I would just like  
22      to reiterate the issue about studying the effect  
23      of whatever is implemented. This was, I guess,  
24      the big problem with the UK is that there was no  
25      systematic way to evaluate what the decision  
26      was -- the consequences of the decision. So it  
27      might be something the FDA should consider, since  
28      this is such an important topic.

1 DR. WOLFE: If the FDA could get some  
2 information about the feasibility or how quickly  
3 someone -- be interested in getting hydrocodone  
4 approved as a single-ingredient drug.

5 DR. SHRANK: Will Shrank. We spoke about  
6 this at previous NDAC panels, but I wanted to  
7 reiterate how important I think it would be to  
8 establish some sort of standardized dosing  
9 instrument for healthcare. We -- it's difficult,  
10 when you're dealing with different concentration  
11 of liquid, but certainly when you have three  
12 products at home, and each has a different kind of  
13 instrument for delivery of the medication -- and  
14 trying to keep them straight ends up being very,  
15 very complicated, even for a  
16 pharmacoepidemiologist.

17 So I think that that's a really -- a  
18 relative easy fix, and something that we should  
19 take seriously.

20 DR. STERGACHIS: Stergachis. We were  
21 presented with a lot of information from a lot of  
22 different sources, and at times it was difficult  
23 to track, and some kind of a dashboard of metrics  
24 that can be set forth and evaluated over time,  
25 getting back to an earlier comment that we're  
26 recommending a lot of different interventions.  
27 It's going to be hard to separate out what the  
28 effects of any given one will be. But taken in

1 its totality, I think this is an opportunity to  
2 assess what the impact is.

3 And number two is there really wasn't any  
4 discussion with regard to liver monitoring, you  
5 know, and I'm not sure -- you know, as a risk  
6 mitigation strategy, I wondered about what the  
7 role might be of any recommendations in that  
8 regard for acetaminophen.

9 DR. BRULL: Yes. Brull. It seems to me  
10 that the single question that received the  
11 tightest consensus was about the boxed warning,  
12 and in light of the fact that this goes to  
13 physicians, I just want to make sure that some of  
14 the information is also then transferred to  
15 patients. That would be very important. It's not  
16 just the physicians and pharmacists, but the  
17 patients need to know about this. And at some  
18 point they have to take some responsibility for  
19 their care. We want to get them involved.

20 DR. HECKBERT: Heckbert. Just to get  
21 this on the list of question 11 items, two things.  
22 One is, as was brought out by Dr. Omogui,  
23 decreasing the acetaminophen dose in the Rx  
24 combination products, if they stay on the market.  
25 That's very important, if they do stay available.  
26 And regarding the pediatric dosing, I think we saw  
27 some pretty good evidence that a syringe was a  
28 better -- resulting in more accurate dosing, and

1 so I think specifically consideration of a syringe  
2 as the way of doing that pediatric dosing.

3 DR. OLSEN: Olsen. I think everybody  
4 agrees here that education is paramount, and when  
5 you realize that not only do most patients not  
6 realize that Tylenol contains acetaminophen, but  
7 believe that their Motrin contains acetaminophen,  
8 that's your starting point.

9 DR. OMOGUI: Omogui. First of all, I  
10 believe that the labeling shouldn't just highlight  
11 acetaminophen on the list of ingredients; there  
12 should be a clear sticker on the front of the box  
13 that says "contains acetaminophen."

14 Secondly, I believe that we focused on  
15 education at the pharmacy, and we've completely  
16 missed education at the physician's office.  
17 That's where the first line should start from. If  
18 the FDA can consider having downloadable flyers on  
19 their website where they can direct physicians to  
20 download the flyers and put them in their offices,  
21 I think you can get maximum distribution at  
22 minimum cost, because if we can education the  
23 patients right in our offices that, when you're  
24 taking these hydrocodone combinations, you can't  
25 go and take OTC acetaminophen, and it's in a  
26 flyer -- we can easily put it in our office and  
27 they can pick it up and take it with them when  
28 they leave.

1                   Also, again, in terms of removing the  
2                   high-dose acetaminophen/opiate combinations, the  
3                   750, 500 milligrams I think would be a very fast  
4                   and cost-effective way of addressing this problem.

5                   And then, finally, again, I will talk  
6                   about the syringes as a measuring device. I  
7                   believe those measuring cups are -- lead to a lot  
8                   of dosing inaccuracies if you're talking about the  
9                   pediatric population. That's also a very  
10                  cost-effective and fast way to -- to bring those  
11                  doses to what they should be and to minimize  
12                  overdosing. Thank you.

13                  DR. TODD: Knox Todd. I think I'd just  
14                  like to make a comment regarding context. The FDA  
15                  has given out many messages over the last ten  
16                  years, necessarily, if one looks at risks of  
17                  non-steroidals, COX-2s and cardiovascular risk,  
18                  opioids, the opioid abuse issue, and acetaminophen  
19                  hepatotoxicity -- and I think there's a risk --  
20                  the pain community, both patients and physicians,  
21                  have felt, I think, somewhat whip-sawed by these  
22                  messages over the last ten years, and there's a  
23                  real danger in attempting to -- or poorly  
24                  orchestrating these messages and trying to deliver  
25                  a coherent message.

26                  And as one of our leaders said, we don't  
27                  have the option of not doing everything at once,  
28                  perhaps, and that may be the case, but I would

1 just try to raise that point. I know those of us  
2 on the committee have felt a little whip-sawed  
3 about some of this information, and it's always  
4 difficult to -- to attempt to advise on policy in  
5 the lack of complete information, but it's an  
6 imperfect world.

7 And I would just like to make an argument  
8 for orchestration and coherence within the  
9 messages that go out with a realization of the  
10 problems that we can create by some of these  
11 messages, and the confusion we can perhaps cause  
12 in the public.

13 DR. KWEDER: Can you be a little more  
14 specific?

15 DR. TODD: Well, the -- daily I deal with  
16 patients in the emergency department who are --  
17 have difficulty reaching pain physicians and come  
18 to the emergency department for care. It's a very  
19 fragmented situation, and oftentimes they don't  
20 feel they have access to the kind of medications  
21 perhaps they need, or the care they need.

22 A point was made earlier, I think,  
23 about -- and a very good point -- about  
24 non-pharmacologic approaches to therapy that often  
25 aren't available for our patients, and we fall  
26 back on pharmacy, and with the inherent risk that  
27 goes with any medication.

28 The messages I think are all necessary.

1 I think certainly the messages about  
2 cardiovascular issues with regard to COX-2s, the  
3 GI and renal issues, the opioid abuse issue --  
4 these are all huge. But I think the public  
5 tends -- we're a little confused, I think, with  
6 all these messages.

7 I wish I had the solution for all this --  
8 I don't. But I just wanted to raise that as an  
9 issue for public communications.

10 DR. LEVINE: Levine. I think the alcohol  
11 warning should be strengthened. Alcohol should be  
12 reduced or -- I prefer to see it "no alcohol."  
13 And I think it will save lives, and I think it  
14 will prevent hepatotoxicity.

15 DR. ENGLE: Engle. I just wanted to  
16 reiterate, not to beat a dead horse, but the peds  
17 dosing on the label for children less than two.  
18 What we see in the pharmacy -- we've talked about  
19 toxicity. What I see more commonly is kids grow  
20 out of their doses so quickly at that young age  
21 group. So parents come into the pharmacy. They  
22 say, acetaminophen doesn't work because, you know,  
23 my kid still has pain. And what happens is  
24 they're taking some very low dose because they've  
25 grown out of their dose.

26 So I think it's critical that we get  
27 those dosing instructions on the label so that  
28 that doesn't get the unintended consequence of



1       them moving onto ibuprofen when it's not  
2       necessary.

3               The other thing I'd like to see is the  
4       flow restrictors. I was really intrigued by that.  
5       I thought that was an excellent idea for the  
6       liquid pediatric formulations. Requiring that of  
7       all products, including generics, would be great.

8               And I agree on the standardized dosing  
9       instruments.

10              And the last thing is our media work, or  
11       your messages out to consumers -- I'd like to see  
12       that tested more so we're sure that the messages  
13       are succinct, they're understandable, and that  
14       consumers can grasp what we're trying to say.  
15       Some of the materials we saw as examples yesterday  
16       I think may have been just too complicated and a  
17       little bit long for consumers.

18              DR. MORRATO: Morrato. I ditto the  
19       remarks in terms of the education and coordination  
20       of risk communication that the others have said.  
21       I'd just like to add that I'd like to insurance on  
22       the scale of that education program, that it's  
23       actually sufficient in terms of reach and  
24       frequency, and that the same energy, urgency and  
25       skill set that's used to sell these drugs is also  
26       applied to selling the safety message as well.

27              And that, in terms of the evaluation  
28       plan, that we look not only -- we make a

1 comprehensive, systematic plan as has been  
2 mentioned, but that that includes both tracking of  
3 awareness, knowledge as well as behaviors, as well  
4 as health outcomes in terms of deaths, poison  
5 control calls, ER and hospitalization, and that  
6 it's really comprehensive in tracking things over  
7 time so that it can be actionable, and if further  
8 action is needed, that that gives us the data to  
9 guide that action. Thank you.

10 DR. PROUGH: Prough. I'll pass.

11 DR. WALKER-HARDING: Walker-Harding. I  
12 had two things. One, just to, again, underscore  
13 that it would be nice if the FDA could fast-track  
14 the under two labeling of acetaminophen on the  
15 box, both for consumers and providers.

16 The other thing is when the evaluation  
17 takes place of whatever changes that are  
18 implemented, that there's a breakout for the 12-  
19 to 24-year-old age group so that you can  
20 specifically see if there's any impact in overdose  
21 on this age group so that, in the future, other  
22 refinement for this age group can be addressed  
23 appropriately.

24 DR. KERNS: Two points. I'd tag onto  
25 that another age group that I think was  
26 underrepresented here was older person. I don't  
27 think we should continue to think about older  
28 persons as just older adults. There are

1 differences that need to be taken into  
2 consideration.

3 And, secondly, I think -- I'd like to  
4 recommend a more specific or fine-grained focus on  
5 combination medications that involve  
6 acetaminophen, both prescribed and  
7 over-the-counter medications. I felt we were  
8 making recommendations in a relative vacuum in  
9 terms of information.

10 DR. KIRSCH: Kirsch. Pass.

11 DR. FARBER: Neil Farber, UC San Diego.  
12 I agree with much of what's been said, and so I  
13 won't reiterate that. The one point I would add  
14 is that I think the FDA and industry need to  
15 partner in terms of learning and behavior. That  
16 is not just education, but addressing the  
17 attitudes and skills among patients as well as  
18 addressing their individual behaviors in some kind  
19 of fashion.

20 DR. LORENZ: Lorenz. I think, as we  
21 struggle to build a system out of the incoherent  
22 pieces of healthcare in the United States, one  
23 thing that shouldn't be lost is that this has been  
24 a tremendous opportunity to consider priorities  
25 that should inform research.

26 And I worry that the next iteration of  
27 this discussion will suffer the same limitations  
28 that we've experienced today. And I think that

1 where it's not explicitly prohibited, it's  
2 incumbent on this meeting to inform, through  
3 creative leadership, work that NIH does, work that  
4 Department of Veteran Affairs does and work that  
5 private industry does in specifically guiding  
6 priorities and comparative effectiveness in  
7 clinical research and drug development. And I  
8 hope that that message won't be lost.

9 DR. KRAMER: Judith Kramer, Duke  
10 University. I have three points. The first point  
11 overlaps a little with what Dr. Lorenz just said.  
12 It seems to me that we were limited a lot today by  
13 lack of information about effectiveness --  
14 dose-ranging information about effectiveness of  
15 acetaminophen for mild to moderate pain. And I  
16 think the agency and independent agencies, like  
17 the NIH and academics, should be encouraged to do  
18 studies, including 325, 500, 600 and 1,000, for  
19 the types of pain that are -- that these products  
20 are actually used for in practice.

21 And I don't mean -- you know, I  
22 understand the value of a validated pain model  
23 where you know you can distinguish. But if it's  
24 not the target population and the indication  
25 you're going to treat, the relevance and  
26 generalizability of that information is  
27 questionable. So I would encourage that study.

28 Number two, I think that if the anything

1 decides to take what I think was the predominant  
2 recommendation to lower the tablet size and the  
3 maximum single dose, that that change should be  
4 seen as an opportunity to educate the public about  
5 why that change is being made and inform them  
6 about, you know, yes, this drug is safe for your  
7 tummy relative to ibuprofen and NSAIDs, but it may  
8 not be safe for your liver if you take more than  
9 the recommended dose -- and to make clear, this is  
10 why we're reducing it.

11 Now, if you coupled that with information  
12 about effectiveness so that you could reassure  
13 them that they're not going to lose a lot of  
14 effectiveness, it would even be more powerful.

15 And number three, I second -- I'm sorry;  
16 I forgot your name -- Dr. Covington, I think. I  
17 think we should petition the FTC to add a warning  
18 for patients directly about the liver  
19 complications.

20 DR. NELSON: Lewis Nelson. Obviously  
21 education is important, and it's hard to say that  
22 there's no role for it, but I am always amazed at  
23 how difficult it is to get people to understand  
24 things that are, you know, much worse for them  
25 than acetaminophen hepatotoxicity might be. And  
26 you could put cigarettes and seat belts -- and you  
27 can go down the list.

28 And I'm afraid that education is not

1 sufficient -- and the word that we use today is  
2 engineering; some people call it mechanical  
3 controls -- there's got to be other systems, fixes  
4 put in place to prevent these types of things from  
5 happening. We discuss some of them when we talk  
6 about these syringes and flow limiters, and we  
7 talk perhaps some administrative fixes, like  
8 pediatric-specific dosing.

9 I think, though, that to rely too much on  
10 medication guides and patient education would be a  
11 mistake. Although they shouldn't be ignored, I  
12 don't think they should be relied on completely.

13 DR. BENOWITZ: Benowitz. I think, in the  
14 short term, I would second the people who  
15 nominated the idea of reducing the acetaminophen  
16 dose in opioid combinations, because I think  
17 that's the single thing that could make the  
18 biggest impact in the shortest time in terms of  
19 liver toxicity.

20 Second issue that I bring up as sort of a  
21 pet peeve of mine, trying to encourage generic use  
22 of drugs among medical students and residents, the  
23 McNeil advertisements for Tylenol, when they  
24 differentiate Tylenol from all other acetaminophen  
25 products, it's really confusing for the consumer  
26 because, you know, the ads always say that Tylenol  
27 is different.

28 And as long as that's being advertised

1       that way, people are going to believe that it's  
2       different, and they need to understand the other  
3       message, that acetaminophen is acetaminophen. And  
4       so I don't know what FDA can do about that, but I  
5       think there's really a mis -- a harmful message  
6       being communicated by current advertising.

7               DR. GRIFFIN: Marie Griffin. I would  
8       second Neil's point about making the combinations  
9       safer, either by lowering the acetaminophen dose,  
10      or by other labels.

11             Secondly, I think that moderately severe  
12      chronic pain is a huge problem, and we don't have  
13      good answers to it, and that's why there's so much  
14      use of this medication, and that there needs to be  
15      clinical trials that address alternative  
16      therapies, and that's a high priority.

17             And, third, I think we need nationally  
18      representative data that is able to evaluate any  
19      changes we make, or look at baseline on these kind  
20      of toxicities and be able to evaluate whether the  
21      changes we make in OTC prescribing or in  
22      prescription prescribing makes a difference.

23             DR. RAJA: Srinivasa Raja. While I think  
24      I agreed with the general opinion that the single  
25      dose should be lowered to a maximum of 650, I was  
26      a little bit concerned that the alternative  
27      provided for the 500-milligram dose was only by  
28      either prescription or none. I felt that -- you

1 know, an alternative was suggested so that a  
2 significant portion of older patients who have the  
3 chronic osteoarthritis may still have access to  
4 it, maybe by providing a 500-milligram OTC that's  
5 not easily available on the counter, but available  
6 only with the pharmacist behind the counter. And,  
7 you know, this allows an opportunity for clearly  
8 discussing the specific concerns, warn the patient  
9 and educate the patient.

10 So one possibility is to have the  
11 500-milligram dose available but behind the  
12 counter.

13 DR. COVINGTON: Covington. I would like  
14 to see the elimination of the narcotic combination  
15 products that contain more than 325 milligrams of  
16 acetaminophen per pill. I would like for us to  
17 petition to require warnings on the  
18 over-the-counter products that contain  
19 acetaminophen. And as a person who has exchanged  
20 cigarettes for seat belts, I'm much less  
21 nihilistic about education than some.

22 DR. LANDIS: Landis. My first comment  
23 has to do with OTC packaging. The products that  
24 Dr. Nelson has up front -- if you look at them,  
25 the font size on that is very small. I know I'm  
26 getting older; it's harder to read. But even as a  
27 practitioner, it's very hard to navigate the  
28 information that's on a package. There's no



1 differentials with font -- and the essential  
2 information that's necessarily for the patient I  
3 don't think is easy to find, even for me at times  
4 when I'm trying to guide a patient through it.

5 So somehow is -- looking at what is  
6 actually going on the packaging and what we can do  
7 to make sure that the consumer is understanding it  
8 better, and making pharmacists and physicians a  
9 little bit easier to access and get that  
10 information to the patient.

11 Tablet limits. I know that that's in the  
12 information that's on those containers, but I  
13 would like to see it be more dominant, both on  
14 packages and on prescription labels. I think that  
15 that would go a long way -- something very easy  
16 for the consumer to see -- limit 8 per day -- not  
17 up to, but limit 8 per day, or 6 per day, or  
18 whatever it is -- and having that in place. I  
19 consider that one of the safety things that we can  
20 put in place real easily.

21 And then the third thing is looking at  
22 more research to see how much of this the consumer  
23 is really comprehending on these changes that we  
24 put in place, or not put in place. I think we  
25 really have to understand, what is it that the  
26 consumer understands? I still think they don't  
27 know what acetaminophen is. You know, we spent a  
28 lot of time talking about, you know, spelling it

1 out on a label when, in fact, a lot of them come  
2 in and they don't understand that term. It's too  
3 long. It's too big. And they don't understand  
4 APAP. So what other kinds of things can we do to  
5 get the consumer up to speed on it?

6 So I would like to see more research in  
7 that area.

8 DR. EISENACH: Eisenach. I think there's  
9 a couple ways we could reach out to physicians.  
10 One of them is, once the FDA decides what they're  
11 going to do with all this information, I think a  
12 "Dear Doctor" letter would be very useful,  
13 highlighting the importance of some of these  
14 decisions.

15 And, secondly, as an editor of the main  
16 journal in our specialty, I know that the  
17 anesthesia community has interacted well recently  
18 with the FDA in publicizing the key findings, and  
19 summarizing the key findings of meetings such as  
20 this. Probably the anesthesia community is not  
21 the most important community for you to reach, but  
22 you might consider this with other journals in  
23 other specialties.

24 DR. ZELTERMAN: Dan Zeltermann. I'm  
25 amazed, after two days of deliberations, the lack  
26 of clinical data that was actually presented here.  
27 We're actually discussing on so little  
28 information. Everything is based on anecdotal

1 information, the suicide reports, the reports from  
2 the emergency department -- all of this is just  
3 anecdotal.

4 I work -- this is a little anecdote. I  
5 work in cancer research. The drugs we use are  
6 extremely toxic. There's extensive studies of the  
7 toxicity profiles before they ever talk about  
8 efficacy.

9 So I would like to see NIH having some  
10 clinical trials sponsored where we can actually  
11 study clinical data efficacy and safety of this  
12 widely used drug.

13 DR. CHOJKIER: Mario Chojkier. I have a  
14 similar comment focused on -- a study may be  
15 extremely valuable for the millions of Americans  
16 with chronic liver diseases. The drug clearly  
17 metabolizes in the liver. I'm not aware of any  
18 detailed information about pharmacokinetics even  
19 in this population. The majority of liver  
20 specialists don't know even what's the dose to  
21 give to a patient with chronic liver disease.

22 Arbitrarily, most of us have cut the dose  
23 by 50 percent, the maximum dose -- 2 grams per  
24 day. But these type of studies, if they can be  
25 orchestrated by the FDA, together with industry,  
26 will be extremely valuable to figure out what is a  
27 safe and efficacious dose for millions of  
28 Americans.

1 MS. EICHNER: Marilyn Eichner, patient  
2 representative. I know that education isn't the  
3 only part, but I believe education is a huge part.  
4 I think if we can educate America on how we're  
5 going to switch from analog TV, then we --  
6 industry has a huge responsibility in educating  
7 the public on acetaminophen -- and most people  
8 don't even know what that means -- because almost  
9 in every household there's a TV.

10 DR. VAIDA: Allen Vaida, ISMP. Just a  
11 couple of things that I think we should focus  
12 attention. One is the strength. The strength of  
13 the acetaminophen should be put on the front  
14 label, which is not on there, although -- on the  
15 combination products, and probably the strength of  
16 all the combination products.

17 Also, the FDA should re-look at how the  
18 labeling is done because, as someone mentioned  
19 before, in looking at the products that have been  
20 passed around, especially the liquid -- hopefully  
21 that's not the final package, because you could  
22 hardly see the acetaminophen on there. It's in  
23 the background, and it's very hard to read.

24 Second thing is the standard dosing  
25 devices with the flow restrictors that someone  
26 else also mentioned should be looked at.

27 And, finally, must include non-steroidals  
28 in any of the recommendations that we're looking

1 at with combination products and some of limits  
2 and that because what we see -- what -- our  
3 organization -- that sometimes people spend a lot  
4 of time on one focus, and something that's so  
5 similar, they'll just wait, and then something  
6 will happen at that. So I think that's very  
7 important.

8 DR. MARKMAN: John Markman. First, I'd  
9 just like to thank the agency for convening this  
10 meeting and an impressing briefing document that  
11 takes on a very complex set of issues.

12 Secondly, I'd like to underscore a point  
13 which has been made by several folks regarding  
14 reducing the dose of acetaminophen in combination  
15 opioids.

16 And, lastly, I'd like to say that nurse  
17 practitioners and physician's assistants are  
18 increasingly in the front lines of clinical care,  
19 and they have a unique perspective and unique  
20 training and vast experience, and I think they  
21 should be more highly represented at forums like  
22 that.

23 MS. DAY: Ruth Day. I agree with many of  
24 the things that people have already said, so I'll  
25 just mention two others.

26 We were asked about the maximum dose for  
27 OTC products, and we were not asked about the  
28 maximum dose for Rx products. And I think that

1 something needs to be said about both so we don't  
2 inadvertently get dose creep, as somebody talked  
3 about previously. So a maximum dose in both areas  
4 of the medications.

5 The other comment, throughout the meeting  
6 sometimes things have come up about pictograms,  
7 and they look great, and you have a little  
8 criticism when someone adds something and so on --  
9 very thorough testing of any of these would need  
10 to be done. We have tested a lot of the standard  
11 ones from the United States Pharmacopeia  
12 compendium of pictograms that have been vetted and  
13 vetted and vetted, and we get some kind of  
14 shocking results. There's one with a picture of a  
15 pregnant woman with a question mark over the head,  
16 which is supposed to be, are you pregnant,  
17 planning on being pregnant, et cetera -- tell your  
18 physician. And we have people with the wildest  
19 interpretations, such as, she's wondering whether  
20 she should tell her boyfriend.

21 So pictograms are a great possibility,  
22 but very careful testing beyond what is normally  
23 done before going forward on any of that, please.

24 DR. POLLOCK: Pollock. Dosing guidelines  
25 for kids under two, and standardized delivery  
26 devices.

27 DR. COOPER: I'd like to introduce a  
28 pictogram of an exclamation point for the dosing

1 instruction for kids under two. I feel like  
2 that's consistent with our charge to look at ways  
3 to reduce liver injury and also will improve  
4 overall the ability for us to care for these young  
5 children.

6 DR. WATTS: Dorraine Watts, Uniformed  
7 Services University. I guess as a nurse and a  
8 statistician, I have a little bit different point  
9 of view. As many have pointed out, we have sort  
10 of a lack of data -- and one of the biggest lacks  
11 I see is nobody has actually asked the patients  
12 why they're taking the wrong dose, why did you  
13 overdose on this medicine?

14 We've got some information from the  
15 clinicians, but nobody has really gone back to the  
16 source and said, why did you take the wrong  
17 medicine? Why did you take too much of it?

18 I think we really need, as Dr. Lorenz and  
19 Dr. Kramer both pointed out, more research into  
20 what -- the root cause of this so we can then  
21 engineer solutions that actually address what the  
22 problem is as opposed to keeping guessing why  
23 people are doing this.

24 DR. HERTZ: Ed Krenzelok. And you're  
25 probably all wondering what the 35th guy is going  
26 to say, after everybody else has said this. But I  
27 do have something to say.

28 All of you have come up with brilliant

1 ideas, but I can tell you that every one of your  
2 ideas will fail at one point or another. And so  
3 my solution is that we have to respond to these  
4 failures when they do occur.

5 Remember we have a consortium of poison  
6 centers in the U.S. that all have the same number,  
7 1-800-222-1222. Dial that number; it takes you to  
8 the nearest poison center in the U.S.

9 So I'd like to encourage industry and the  
10 FDA to work with the American Association of  
11 Poison Control Centers, and also help fund poison  
12 centers, so that they can address the needs of  
13 these patients who overdose on acetaminophen  
14 products and other products. We're really the  
15 first line in caring for these.

16 So keep that number in mind, and try to  
17 figure out a way, maybe, to work more closely with  
18 poison centers.

19 DR. NELSON: Thank you. And we're right  
20 on time.

21 So the results are in. Are they -- let's  
22 see if we can show them.

23 So question [sic] number 1 is actually  
24 complicated because you could have chosen 1a and b  
25 together, or 1a or 1b. So question 1 is a  
26 combined product. There were nine people that  
27 voted for that option as the highest priority. 1a  
28 alone was three. And 1b alone was one.



1                   For option number 2, zero.

2                   For option number 3, one.

3                   For option number 4, seven, which was the  
4 boxed warning.

5                   For option number 5a, eliminate OTC  
6 combination products, two.

7                   And 5b, which is eliminate prescription  
8 acetaminophen combination, was seven.

9                   For 6, which was OTC liquid formulations,  
10 was seven.

11                  And then for none of the above, there  
12 were zero.

13                  I'm not sure you could read that any  
14 better than I just read it. And they're not in  
15 order, so don't try to go -- the order is 1, 1a,  
16 1b, 2, 5a, 6, 5b, 3, 4, and then none of the  
17 above.

18                  Does that make sense to everybody? I'm  
19 sure it didn't help. That was the order going  
20 across. I read them in numerical order, but the  
21 order going across --

22                  MS. FERGUSON: These results will be  
23 hanging outside of the door here so you can  
24 actually see them. We realize that, with this  
25 number of people voting, that it would be very  
26 hard to display them on the screen, but we're  
27 trying here, and they will be posted outside.

28                  DR. NELSON: Right.

1                   To the FDA, are there any points you want  
2                   to ask, bring up, discuss with this or --

3                   DR. KWEDER: I actually think that your  
4                   vote here really reflects the discussion, and so I  
5                   don't think that we have any further questions. I  
6                   think the -- our intent was to get a general view  
7                   of where you think we ought to place our efforts.  
8                   I think it's pretty clear that, overall, there is  
9                   a great deal of interest in examining the doses  
10                  that are currently available, as well as OTC  
11                  liquid formulations, and considering the pros and  
12                  cons of how to deal with combination acetaminophen  
13                  products that are prescription and, for those  
14                  prescription products, seriously considering how  
15                  to better inform patients and providers through  
16                  the use of a boxed warning.

17                  Those are places for us to begin.

18                  DR. NELSON: Well, thank you. Thanks to  
19                  the FDA for hosting this meeting. Thanks to those  
20                  participating in the meeting, and to the audience,  
21                  to the sponsors and our special guests, and a  
22                  special thanks to Elaine for doing a yeoman's job  
23                  here.

24                  Thank you, all.

25                  (Whereupon, the proceedings at 4:22 p.m.  
26                  were concluded.)

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