U.S. Food and Drug Administration

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Summary Minutes of the Joint Meeting of the Drug Safety and Risk Management Advisory Committee,
Nonprescription Drugs Advisory Committee,
and the Anesthetic and Life Support Drugs Advisory Committee
June 29 and 30, 2009

Location: The Marriott Conference Centers, University of Maryland, University College Inn and Conference Center, 3501 University Blvd. East, Adelphi, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the June 29 and 30, 2009 Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee of the Food and Drug Administration were approved on August 19, 2009.

I certify that I attended the June 29 and 30, 2009 Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

----------/s/----------

Elaine Ferguson M.S.
Designated Federal Official

----------/s/----------

Lewis Nelson, M.D.
Acting Committee Chair

Joint Meeting of the Drug Safety and Risk Management Advisory Committee,
Nonprescription Drugs Advisory Committee,
and the Anesthetic and Life Support Drugs Advisory Committee
June 29 and 30, 2009

The Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee, Center for Drug Evaluation and Research met on June 29-30, 2009 at the Marriott Conference Centers, University of Maryland, University College Inn and Conference Center, 3501 University Blvd. East, Adelphi, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. This was a voting meeting. There were approximately three hundred and fifty (350) persons in attendance.

Issue: The primary topic area for discussion was how to address the public health problem of liver injury related to the use of acetaminophen in both over-the-counter (OTC) and prescription (Rx) products. FDA recognizes that acetaminophen is an important drug used to treat pain and fever in both settings and is not seeking to remove it from the market. The risk of developing liver injury to the individual patient who uses the drug according to directions is very low. However, acetaminophen containing products are used extensively making the absolute number of liver injury cases a public health concern.

Attendance:

Drug Safety and Risk Management Advisory Committee

Members Present (Voting): Susan R. Heckbert, M.D., Ph.D., Judith M. Kramer, M.D., M.S., Sidney M. Wolfe, M.D. (Consumer Representative)

Special Government Employee Consultants (Voting): William Cooper, M.D., Ruth S. Day, Ph.D., Edward Krenzelok, Pharm.D., Elaine Morrato, DrPH M.P.H., Lewis Nelson, M.D. (Acting Chair), Andy Stergachis Ph.D., R.Ph., Allen Vaida, Pharm.D.

Nonprescription Drugs Advisory Committee

Members Present (Voting): Neal L. Benowitz, M.D., Janet P. Engle, Pharm.D., FAPhA, Neil J. Farber, M.D., Walid F. Gellad, M.D., M.P.H., Marie R. Griffin, M.D., Winifred A. Landis, R.Ph., C.D.E., William H. Shrank, M.D., M.S.H.S., Leslie R. Walker-Harding, M.D., Dorraine D. Watts, Ph.D., R.N.

Industry Representative Present (Non-Voting): Lorna C. Totman Ph.D., DABT (Acting Industry Representative).

Anesthetic and Life Support Drugs Advisory Committee

Members Present (Voting): Sorin J. Brull, M.D., Jeffrey R. Kirsch, M.D., Osemwota A. Omoigui, M.D. (Consumer Representative), Julia E. Pollock, M.D., Donald S. Prough, M.D., Daniel Zelterman, Ph.D.

Special Government Employee Consultants (Voting): Edward Covington, M.D., Richard DeNisco, M.D., M.P.H., James Eisenach, M.D., Robert D. Kerns, Ph.D., Karl Lorenz, M.D.,M.S.H.S., John Markman, M.D., Srinivasa Raja, M.D., Knox H. Todd, M.D., M.P.H.

Industry Representative Present (Non-Voting): Charles H. McLeskey, M.D. (Acting Industry Representative)

Special Government Employee Consultants (Voting):

Mario Chojkier, M.D., Marilyn Eichner (Patient Representative), Robert Levine, M.D., Nancy J. Olsen, M.D.

Guest Speakers (Non-Voting): William Bower, M.D., F.I.D.S.A., Daniel S. Budnitz, M.D, M.P.H., CDR, USPHS, Paul Dargan, M.B. B.S. FRCPE FACMT, Professor Keith Hawton, D.Sc. D.M. FRCPsych, Laura James, M.D., William Lee, M.D.

FDA Participants (Non-Voting): Sandra L. Kweder, M.D., Charles Ganley, M.D., Gerald Dal Pan, M.D., M.H.S., Sharon Hertz, M.D.

Attendance continued….

Designated Federal Official: Elaine Ferguson, M.S.

Open Public Hearing Speakers:

June 29, 2009: Rebecca Burkholder, J.D.(National Consumers League), Margalit Ratner, Benard Dreyer, M.D. (American Academy of Pediatrics Health Literacy Project Advisory Committee), Timothy Davern (American Association for the Study of Liver Diseases), Kerry Lane, M.D., Paul Desjardins (Wyeth Consumer Health Care).

June 30, 2009: Anthony Temple, M.D., Thomas Clark, R.Ph., M.H.S., C.G.P., (American Society of Consultant Pharmacists), Pamela Snow (Arthritis Foundation), Carmen Catizone (National Association of Boards of Pharmacy), Kevin Nicholson, R.Ph., J.D. (National Association of Chain Drug Stores), John Sebby (National Pain Foundation), Melissa Henry (Mallinkrodt) and Rebecca Drake.

The agenda was as follows:

June 29

8:00 a.m.	Call to Order Introduction of Committee	Lewis Nelson, MD Acting Chair, DSaRM Gerald Dal Pan, MD
	Conflict of Interest Statement	Elaine Ferguson, MS Designated Federal Official, DSaRM
8:10 a.m.	FDA Acetaminophen Background and Overview	Gerald DalPan, MD Director of Office of Surveillance and Epidemiology CDER/OSE
8:25 a.m.	FDA Regulatory Information: Regulation of Acetaminophen Drug Products	Arlene Solbeck, MS Senior Regulator Review Scientist Office of NonPrescription Products OND/DNRD
8:35 a.m.	FDA Marketing Information: OTC and Rx Acetaminophen Market Overview	Laura Governale, Pharm D Drug Utilization Data Analysis Team Leader Division of Epidemiology, Office of Surveillance and Epidemiology OSE/DEPI
8:45 a.m.	Metabolism/Toxicology Background	Laura James, MD Guest Speaker Professor, Department of Pediatrics University of Arkansas for Medical Sciences Section Chief, Clinical Pharmacology and Toxicology Arkansas Children's Hospital
9:05 a.m.	Committee Questions to the Speakers	
9:15 a.m.	Consumer Health Care Products Assoc.	Linda Suydam, DPA President, Consumer Healthcare Products Association James H. Lewis, MD Professor of Medicine and Director of Hepatology. Georgetown University Medical Center
9:45 a.m.	Denver Health: The Safety of Acetaminophen During Therapeutic Use	Richard C. Dart, MD Rocky Mountain Poison and Drug Center-Denver Health and Hospital Authority; University of Colorado School of Medicine

10:00 a.m.	Break 15 min break Agenda continued…	
10:15 a.m.	*McNeil Consumer Healthcare* Introduction and McNeil Position	Edwin Kuffner, MD Senior Director Medical Affairs McNeil Consumer Healthcare
	Acetaminophen Efficacy Among Doses	Cathy Gelotte, PhD Senior Director Clinical Pharmacology McNeil Consumer Healthcare
	Proposed Risk Mitigation Framework Based on Root Cause Analysis	Edwin Kuffner, MD Senior Director Medical Affairs McNeil Consumer Healthcare
	Epidemiologic-based Switching Model	Kenneth Rothman, DrPh Vice President, Epidemiology Research, RTI Health Solutions
11:15 a.m.	Cadence Sponsor Presentation	James B. Breitmeyer, MD Chief Medical Officer
11:30 a.m.	Committee Questions to Industry	Cadence Pharmaceuticals, Inc.
12:00 p.m.	Lunch	
	Safety	
1:00 p.m.	Update on Acute Liver Failure Study Group	William Lee, M.D Guest Speaker Holder of the Meredith Mosle Chair in Liver Diseases. UT Southwestern Medical Center at Dallas
1:20 p.m.	Acetaminophen-related Emergency Department Visits -- Findings from the National Electronic Injury Surveillance System, 2004-2007	Dan Budnitz, MD, MPH, CDR, USPHS Guest Speaker Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention CDC
1:40 p.m.	CDC Data: Acute Liver Failure and Acetaminophen	William Bower, MD, FIDSA, CDR, UPHS Guest Speaker Office of Blood, Organ, and other Tissue Safety Division of Healthcare Quality Promotion, NCPDCID, CCID Centers for Disease Control and Prevention (CDC)
1:50 p.m.	FDA Data: Characterization of Acetaminophen Overdose and Related Hepatotoxic Events	Angelika Manthripragada, PhD Epidemiologist, Office of Surveillance and Epidemiology OSE/DEPI
2:05 p.m.	Committee Questions to Speakers	
2:35 p.m.	Single-ingredient acetaminophen dose-response data in adults	Christina Chang, MD Medical Officer, Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products OND/ONP/DNCE
2:50 p.m.	Rx. Acetaminophen Combination Products	Jane Filie, MD Medical Officer, Division of Analgesia, Anesthesia and Rheumatology Products OND/DAARP
3:05 p.m.	Break	
3:20 p.m.	Education Outreach: FDA Consumer Education on the Safe Use of Acetaminophen	Ellen Frank Director, Division of Public Affairs, OTCOM/DPA

Agenda continued…

3:35 p.m.	OTC Use Behavior: Comprehension and Behavioral Factors Associated with OTC Medication Misuse	Laura Shay, PhD, Captain USPHS Social Science Analyst, Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products OND/ONP/DNCE
3:45 p.m.	Committee Questions to Speakers	
4:00 p.m.	Open Public Hearing	
5:00 p.m.	Adjourn	

June 30th

8:00 a.m.	Call to Order Introduction of Committee	Lewis Nelson, MD Acting Chair, DSaRM
	Conflict of Interest Statement	Elaine Ferguson, MS Designated Federal Official, DSaRM
8:10 a.m.	UK analgesic pack regulation: Background, rationale and impact	Professor Keith Hawton DSc DM FRCPsych Guest Speaker Director, Centre for Suicide Research University Department of Psychiatry Warneford Hospital Oxford, UK
8:30 a.m.	The impact of the 1998 UK paracetamol pack-size legislation on paracetamol poisoning	Dr Paul Dargan Guest Speaker Clinical Director for Toxicology Guy's and St Thomas' NHS Foundation Trust London, UK
9:10 a.m.	Committee Questions to Speakers	
9:25 a.m.	Open Public Hearing	
10:25 a.m.	Break	
10:40 a.m.	FDA Presentation of Options and Questions	Susan S. Johnson, PhD Associate Director ONP OND/ONP
10:55 a.m.	Committee Discussion and Vote	
12:15 p.m.	Lunch	
1:15 p.m.	Committee Discussion and Vote	
3:00 p.m.	Break	
3:15 p.m.	Committee Discussion and Vote	
4:30 p.m.	Adjourn	

Questions to the Committee

For each question, the relevant Option from the background package's Options Paper is presented in a text box. Although the order of presentation has been changed, these options are numbered as they appear in the Options Paper.

A set of General Considerations for you to take into account in your discussion and decisions of all questions is provided on the last page. In addition, other factors that you should take into account are listed and you may identify other factors that you find relevant.

Nonprescription Products

FROM OPTIONS PAPER: "OPTION 1a"

Reduce the current dosage strengths of acetaminophen in nonprescription products. This could include the maximum adult daily dose, maximum single adult dose, and maximum dosage strength.

In addition to the General Considerations, consider the following:

- Efficacy provided by the higher single and daily doses
- Availability of different doses for various clinical indications
- Additional safety concerns posed by the availability of higher strength acetaminophen products compared to lower strength products
- Balance of efficacy benefit with safety concerns
- How the "best" dosage should be determined
- FDA will consider responses to Questions 1 and 2 when determining whether to reduce the current dosage strengths of acetaminophen in prescription products.

Question 1 (Vote)
Do you recommend that the maximum total daily dose (4 grams/day) of acetaminophen in nonprescription single ingredient and combination products be lowered?

11 members voted for A – Yes, I recommend this change and consider it a high priority
10 members voted for B – Yes, I recommend this change
16 members voted for C – No, I do not recommend this change

Question 2 (Vote)
Do you recommend that the maximum nonprescription single adult dose be limited to 650 mg?

12 members voted for A – Yes, I recommend this change and consider it a high priority
12 members voted for B – Yes, I recommend this change
13 members voted for C – No, I do not recommend this change

The following views were expressed by committee members during the discussion of question 1 and question 2. Please refer to the transcript to obtain all of the committee member's comments.

- *Although the toxicity data for the 4 gram/day dose was not compelling it is clear that there is a small window between the dose that is therapeutic and the dose that may be toxic.*
- *The toxicity data for the 4 gram/day dose is compelling.*
- *There is not enough data to know if overdosing is occurring with nonprescription products or prescription products.*
- *There is not enough efficacy data to weigh the benefits and risk associated with the various doses when used to treat various types of pain.*

- *The potential for unintentional overdosing is most likely to occur when the patient is standing in front of a shelf making a decision on their own.*

- *Will a change really make a difference? When many people are already aware that 4000mg/day is ok.*
- *Acetaminophen is viewed as a drug that is dosed every 4 hours. .*
- *There is a simplicity about saying and remembering 4000 mg versus 3250 mg*
- *Physicians can prescribe higher doses. Patients who need higher doses should be under a physicians care.*
- *The addition of other formulations (500mg, 650mg and 1000mg tablets) may have contributed to "dose creep".*
- *Limit the amount per tablet, a person is less likely to exceed the recommended dose.*
- *Question 1 and 2 are tied together, the dose that is chosen will inform the amount of drug in each tablet.*
- *Concern that the public will view dosing as "titratable", that you can increase the dose as needed. Using 325 mg tablets, with instructions that say take one tablet for (X), take two tablets for (X),and take three tablets for (X)*

FROM OPTIONS PAPER: "OPTION 1b"

If OTC dose were reduced, switch of current higher dosage to prescription status.
This could be 500 mg per tablet, 1000 mg per maximum dose
and/or 4 grams as the maximum daily dose.

In addition to the General Considerations, consider the following:

- Patient population(s) under healthcare providers' care who may require the current maximum strength of acetaminophen

Question 3 (Vote)

If the current doses of nonprescription products are lowered, do you recommend that the current maximum dosage of acetaminophen (i.e., 2 x 500 mg) be switched to prescription status?

8 members voted for A – Yes, I recommend this change and consider it a high priority
18 members voted for B – Yes, I recommend this change
11 members voted for C – No, I do not recommend this change

The following views were expressed by committee members during the discussion of question 3. Please refer to the transcript to obtain all of the committee member's comments.

- *The 1000 mg tablet is useful for those requiring the higher dose.*
- *Consider the associated cost for patients, physicians and the already burdened health care system.*
- *Consider the unintended consequences when it has already been expressed that some prescribers are not practicing within reasonable standards of care.*
- *What signal are we giving? If patients know that there are higher strength tablets (500mg). We know from existing models that patients will take higher doses.*
- *There are already existing models that work, famotidine and ibuprofen.*
- *I feel comfortable with patients being able to obtain 500mg tablets without an office visit.*
- *Making 500mg tablets prescription only would be a barrier to care, particularly for the elderly.*
- *Another option would be to make the 500mg tablets available through Pharmacists*
- *Making the 500mg tablets prescription is not necessarily a bad thing, I want to know when my patients are hurting.*
- *Making the 500mg tablets prescription is a compromise, making the formulation available and giving the practitioner an opportunity to discuss the toxicity with the patient.*

FROM OPTIONS PAPER: "OPTION 2"

Establish pack size limits for OTC acetaminophen products.

In addition to General Considerations, consider the following:

- The impact of the U.K. experience with mandated pack size restriction and no mandated sales restriction
- Relevance of the U.K. experience to the U.S. marketplace
- How FDA should determine an appropriate OTC pack size
- Public health and safety consequences of the potential for increased use of other analgesics

Question 4 (Vote)

Do you recommend that pack size limits be implemented for nonprescription acetaminophen products?

2 members voted for A – Yes, I recommend this change and consider it a high priority
15 members voted for B – Yes, I recommend this change
20 members voted for C – No, I do not recommend this change

The following views were expressed by committee members during the discussion of question 4. Please refer to the transcript to obtain all of the committee member's comments.

- *If pack size of acetaminophen is restricted, consideration should be given to limiting pack size of nonsteroidals (ibuprofen and naproxen) and salicylates (aspirin) to avoid an inadvertent, unintentional, impact on safety.*
- *To prevent overdose the pack size would have to be less than the pack size of 16 grams used in the United Kingdom (UK).*
- *Pack size in locations that do not have a pharmacy should be restricted.*
- *Consider the negative impact that limiting the pack size may have on: the elderly who are not mobile, people who have to take acetaminophen for chronic pain, people who live in rural areas and large families.*
- *A package size of 1000 tablets in a bottle gives the wrong message.*
- *There would be an educational value to saying that you will not be able to purchase packages with more than X number of tablets anymore.*
- *There is no data to support the assumption that a large package sizes gives the wrong message.*
- *Skepticism that decreasing the pack size will have any impact on preventing liver toxicity, given that there is conflicting data from the UK experience, even with their large educational campaign.*
- *Using a 325 mg tablet, a one month supply for a chronic arthritis patient would be 300 tablets.*
- *Maybe there should be a 500 tablet "osteo pack" that you can get from the pharmacy.*
- *The UK presenter showed that restricting pack size does not prevent you from buying more than one package.*
- *1000 tablets per bottles are not necessary.*
- *A "no" vote doesn't mean that the member supports a 1000 tablet bottle.*
- *There really isn't any difference between 500 tablets per bottle and 1000 tablets per bottle.*

FROM OPTIONS PAPER: "OPTION 5a"

Eliminate nonprescription acetaminophen combination products.

In addition to the General Considerations, consider the following:

- Role of combination products in duplicate dosing of acetaminophen
- Consumer knowledge about presence of acetaminophen in OTC combination products

Question 5 (Vote)

Do you recommend eliminating nonprescription acetaminophen combination products?
2 members voted for A – Yes, I recommend this change and consider it a high priority
11 members voted for B – Yes, I recommend this change
24 members voted for C – No, I do not recommend this change

The following views were expressed by committee members during the discussion of question 5. Please refer to the transcript to obtain all of the committee member's comments.

- *There are some combination products that can't be duplicated using single ingredient products. There may be a need for some combination products.*
- *We were not given any information in the presentations to inform us on this question.*
- *38% of patients, who didn't have any symptoms that would be relived by the use of acetaminophen, took a combination product that contained acetaminophen.*
- *Combination products contributed little to liver toxicity seen with acetaminophen.*
- *10% of fatalities due to acetaminophen were seen with patients taking combination products that contained acetaminophen.*
- *Mortality is less with the combination products because people get sick from the other ingredients.*
- *Not convinced of the efficacy of combination products; but, there is the potential for harm.*
- *Each combination product needs to be assessed, would not want all combinations products to be thought of as "one class"*
    - *Concern for combination products that might be used chronically.*
    - *Acetaminophen with caffeine is a bad combination.*
    - *Evaluate efficacy versus risk of each combination product. There is no information on the benefits/risk for combinations.*
    - *Consider what impact there will be on other combination products that do not contain acetaminophen. Concern that there may be substitution. Just looking at acetaminophen containing products is not enough. Need to look at combination products containing nonsteroidals (NSAIDS) and salicylates.*
- *It is difficult to figure out and explain to patients what does and does not contain acetaminophen.*
- *We are asking too much of patients.*
- *Eliminating combination products is one way to engineer in safety.*
- *Display on the front of the label "contains acetaminophen".*
- *No data was needed to market a combination product, why is data needed to remove these products.*

FROM OPTIONS PAPER: "OPTION 6"

Limit formulations for OTC LIQUIDS.

In addition to the General Considerations, consider the following:

- The OTC monograph does not currently stipulate specific concentrations of acetaminophen liquid formulations
- Dosage administration considerations for pediatric patients of various ages
- Identifying the concentration of acetaminophen liquid that should be made available for children, if only one concentration is allowed

Question 6 (Vote)

Do you recommend that only one concentration of nonprescription acetaminophen liquid be available?
19 members voted for A – Yes, I recommend this change and consider it a high priority
17 members voted for B – Yes, I recommend this change
1 member voted for C – No, I do not recommend this change

The following views were expressed by committee members during the discussion of question 6. Please refer to the transcript to obtain all of the committee member's comments.

- *An adult formulation should be considered, there are other reasons to use liquid formulations.*
- *If there are 2 concentrations an error is likely to occur. In the hospital setting where doses are administered by professionals, errors occur when there are two concentrations*
- *When working with parents there is confusion.*
- *Not convinced that there is a clear benefit to having two formulations.*
- *Clear dosing instructions need to be provided.*
- *Education may have an impact.*
- *The presentation from the first day showed greater accuracy with syringes. Medication cups are difficult to read and there were dosing errors, with medication cups.*
- *Some members preferred a more concentrated formulation. Others preferred the less concentrated formulation stating that if an error occurred there would be less potential for harm.*

Prescription Products

FROM OPTIONS PAPER: "OPTION 5b"

Eliminate prescription acetaminophen combination products.

In addition to the General Considerations, consider the following:

- Currently, the combination products fall under Schedule III. Single ingredient opioid analgesics, by DEA regulation, are regulated as Schedule II and have different prescribing and dispensing requirements.
- Potential safety concerns associated with the drugs that will be used as therapeutic replacements for the opioid-acetaminophen combinations (e.g., NSAIDs, Schedule II opioids.)

Question 7 (Vote)

Do you recommend eliminating the prescription acetaminophen combination products?

10 members voted for A – Yes, I recommend this change and consider it a high priority
10 members voted for B – Yes, I recommend this change
17 members voted for C – No, I do not recommend this change

The following views were expressed by committee members during the discussion of question 7. Please refer to the transcript to obtain all of the committee member's comments.

- *Reduce the strength (number of milligrams) of acetaminophen in the combination products; however, efficacy must be maintained.*
- *Remove the combination products that contain the most acetaminophen.*
- *This is where we can have the greatest impact on preventing drug induced hepatotoxicity.*
- *Concerns about moving hydrocodone from schedule III… which does not require a written prescription from a doctor, the doctor can call the pharmacy and order the medication or can submit an electronic prescription…. to schedule II which requires the doctor to provide a hand written prescription.*
    - *Having to write a prescription for a schedule II medication should make the physician think, "does this patient need an opioid".*
    - *Physicians would likely switch to schedule III combination products that contain nonsteroidals (NSAIDS), rather had write a prescription for a schedule II product. If acetaminophen containing combination products are removed, the same should be considered for nonsteroidal (NSAIDS) schedule III combination products.*
- *Concern about abuse issue when narcotics are given alone and increasing the use of straight opioids*
    - *With oxycodone combination products you don't have the abuse that you have with oxycodone alone.*
- *It is remarkable that there is not more toxicity seen given the high use of hydrocodone combination products.*

- *Physicians in the hospital setting often forget the amount of acetaminophen a patient receives when they prescribe hydrocodone combination products. Patients are often unaware that they are receiving acetaminophen.*
- *There is a need for comparative efficacy studies. A recommendation was made for an evaluation of clinical outcomes of prescribing opioid-acetaminophen combinations vs. an approach where the opioid and acetaminophen are prescribed separately.*
- *There is a need for potent schedule III narcotics that a physician call a pharmacy and order when needed by a patient.*
- *The cost will increase for the patient if they have to purchase hydrocodone by prescription and a bottle of acetaminophen.*
- *The patient will have to take two different medications.*
- *This will have an impact on pain management. The consequence will be negative.*

FROM OPTIONS PAPER: "OPTION 3" and "OPTION 4"

If prescription acetaminophen combination products continue to be marketed, implement additional safety measures by requiring "unit-of-use" packaging and/or additional warning materials.

With "unit-of-use" packaging, products would be packaged by the manufacturer or distributer for sale in a pharmacy, without the product needing to be repackaged. Packaging would display standardized information on the prescription package directed to patients (e.g., prominent display of 'ACETAMINOPHEN' as an active ingredient and a warning about potential liver damage.) and convey a Medication Guide to patients.

A boxed warning could be implemented with or without "unit-of-use" packaging.

In addition to the General Considerations, consider the following:

- FDA recently issued new regulations for labeling OTC products containing acetaminophen to enhance warning information and prominence of identification of 'acetaminophen' as an active ingredient.
- Current pharmacy practices do not require consistent nomenclature and warning information on pharmacy-packaged prescriptions.

Question 8 (Vote)

If prescription acetaminophen combination products continue to be marketed, do you recommend that "unit-of-use" packages be required?

5 members voted for A – Yes, I recommend this change and consider it a high priority
22 members voted for B – Yes, I recommend this change
10 members voted for C – No, I do not recommend this change

Question 9 (Vote)

Do you recommend that FDA require a boxed warning for prescription acetaminophen combination products?

25 members voted for A – Yes, I recommend this change and consider it a high priority
11 members voted for B – Yes, I recommend this change
1 member voted for C – No, I do not recommend this change

The following views were expressed by committee members during the discussion of question 8 and question 9. Please refer to the transcript to obtain all of the committee member's comments.

Clarification to committee: The intent of the unit-of-use package is to assure standardized labeling

- *Conceptually agree that making the information standardized is a good thing*
- *There are many reasons for not dispensing a bottle, intact as is (one-unit of use)*
    - *Patients who want to try a few doses before they purchase a larger supply*

    - *Insurance limits. Practitioners usually order the quantity that will be covered by insurance.*
    - *Pain Physicians are more likely to request a specific amount.*
- *Pharmacists place a patient label on the bottle which would cover up the standardized label*
- *Auxiliary labels are not required, they are determined by the pharmacy. Auxiliary labels are becoming more consistent because the information is included in a printout that is generated for the patient.*
- *Could provide information for other bottles, when smaller quantities are dispensed.*
- *It should be mandated that the ingredients be listed on the patient prescription label in addition to the total number of pills per day that can be taken.*
- *Labeling is a weak intervention*
- *The first time a patient receives a bottle, they are more likely to read the information than if they receive the bottle more than once. The more sporadically the patient receives the bottle the more likely they are to read the label.*
- *When the press writes up the results of the meeting they often state that a black box warning is the highest warning, which will alert people that they need to think about acetaminophen more.*
- *Black box warnings are ignored by health care professionals and will not do much to address the problem.*

Question 10 (Vote)

Overall Ranking of Options

Options related to both Rx and OTC products containing acetaminophen have been discussed. You have already indicated whether you consider each individual option a high priority. To further clarify how FDA should focus its resources to decrease the public health burden of acetaminophen liver toxicity, indicate the single option, including both nonprescription and prescription options, which you recommend that FDA consider its highest priority. If you do not recommend that FDA implement any of the proposed options, please indicate this on the ballot provided.

Nonprescription Products

Note: Options 1a and 1b may be considered a single option or two separate options.

9 members voted for ***Option 1a and 1b****, as a single option.*
3 members voted for **Option 1a** *only* - Reduce maximum dose of OTC acetaminophen
1 member voted for **Option 1b** *only* - Switch current maximum dose of OTC acetaminophen to prescription

0 members voted for **Option 2 -** Establish pack size limits for OTC products

2 members voted for **Option 5a** – Eliminate OTC acetaminophen combination products.

7 members voted for **Option 6 -** Limit OTC liquid formulations

Prescription Products

7 members voted for **Option 5b -** Eliminate prescription acetaminophen combination products

1 member voted for **Option 3 -** Require unit of use packaging for prescription acetaminophen combination products

7 members voted for **Option 4 -** Require a boxed warning for prescription acetaminophen combination products

No member indicated on the ballot, that they did not recommend that FDA implement any of the proposed options.

Question 11 (Discuss)

What other options FDA should consider that have not been discussed in the options provided?

Please refer to the transcript for specific suggestions and additional options that the FDA should consider.

- *Several suggestions were made regarding the need to track and evaluate the interventions that the FDA decides to implement.*
- *Several suggestions were made regarding education programs and changes in labeling.*

- *Several recommendations were made regarding the need for additional studies.*
- *Several recommendations were made regarding decreasing errors in infants and children.*
- *Petition the Federal Trade Commission to have a warning about liver toxicity for patients.*
- *Alcohol warning should be strengthened, should say no alcohol.*
- *Obtain information about how long it would take to get hydrocodone as an individual drug.*
- *Consider overall cost to the health care system.*

The ‘General Considerations’ apply to each of the questions. You may want to tear off this sheet and use it for reference when responding.

General Considerations

- Potential for this change to decrease incidence of liver injury
- Effect on patients (e.g., convenience, monetary factors, education)
- Effect on healthcare practitioners
- Whether the regulatory steps, resources, and time needed to implement this change are merited by the potential impact of the change
- Steps that manufacturers would need to take to support this change
- Other potential consequences of this change that should be anticipated