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December 17, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 01N-0397

SUBJECT: FDA/NTSB Joint Public Meeting on Transportation Safety and Potentially Sedating or Impairing Medications:
Comments on the Safety of OTC Antihistamines and OTC Labeling

To Whom It May Concern:

These comments are submitted to the Food and Drug Administration (FDA) and National Transportation Safety Board (NTSB) in response to the open public comment period relating to the November 14-15, 2001, meeting on "Transportation Safety and Potentially Sedating or Impairing Medications." The Consumer Healthcare Products Association (CHPA) appeared on November 14, 2001, at the FDA/NTSB Joint Public Meeting, proving expert testimony on two panels and participating in the question and answer sessions for interested parties.

CHPA is a 120-year-old trade organization representing the manufacturers and distributors of nonprescription (or over-the-counter, OTC) medicines and dietary supplements. CHPA represents over 95% of the nonprescription medicines market by sales. CHPA members market all the major national brand and store brand antihistamine-containing nonprescription (or, over-the-counter, OTC) products in the United States.

At the time of the submission of these comments, the transcript of the November 14-15 meeting was not available. Since a number of expert witnesses invited by the government were supportive of the perspective and conclusions provided herein, CHPA will be submitting an addendum to these comments, in which we highlight key supportive statements of the expert witnesses. We ask that FDA accept these comments and the forthcoming addendum as information important to the consideration of the safety of OTC antihistamines.

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Outline of Comments

CHPA's comments are organized according the following outline:

I. Overview

Currently marketed nonprescription medicines have been thoroughly studied with respect to their safety profiles. Knowledge about side effects has been evaluated by expert advisory panels either during the OTC Review or prior to marketing of a product switched from Rx to OTC status. The principal OTC medicines which are known to diminish wakefulness and potentially affect performance are the first-generation antihistamines. For this reason, CHPA comments emphasize this class of OTCs. A thorough review of FDA's AER system and other information indicates that there are no unexpected signals of concern relating to accidents associated with OTC antihistamines.

FDA and the Association have had decades-long discussions on many different aspects of OTC drug labeling, the principal form of communication between the manufacturer and consumer on warnings, ingredient content, dosage instructions – so-called "Drug Facts." These CHPA's comments also focus on this aspect of communication, particularly as it relates to OTC antihistamines. OTC antihistamines have appropriate labeling relating to drowsiness and directions of use, and this labeling has recently been made even more consumer-friendly through the FDA final rule on "Drug Facts" labeling.

Pictograms or symbols are potentially confusing, rob scarce label space without a public health benefit to their use being demonstrated, and potentially could lead

consumers to ignore more important warnings for their particular underlying condition. They are unproven in any use situation for OTC medicines.

Neither the available data from FDA's adverse experience reporting system nor the unproven nature of pictograms in an OTC setting provides any support for changes in OTC labels to bring further prominence to drowsiness warnings on OTC antihistamines, either by pictograms, symbols or other means.

Hence, the efforts to address OTC medication use outside of label directions should be aimed at education to build awareness to the need to read the label and follow directions for use and heed warnings. Both CHPA and The Council on Family Health have had a long-standing program to promote the message of "read the [OTC] label," and both organizations plan to continue these efforts. Both groups have also had very successful track records in creating partnerships with government agencies and other groups as a means to promote the "Read the Label" message. CHPA believes it is important to maintain an ongoing program of consumer education on the importance of reading the label.

II. OTC Antihistamines: Types, Extent of Use, and Required Drowsiness Warnings

OTC antihistamines have a long history of safe and effective use when used as recommended on the label.

- Current OTC antihistamines (also called first-generation antihistamines), such as chlorpheniramine and diphenhydramine, have been on the Rx market for more than 50 years and on the OTC market for more than 25 years.
- OTC antihistamines are generally recognized as safe and effective for symptoms relating to colds and allergy, for treatment of nausea, and as a sleep-aid (e.g., see OTC Final Monographs).[1]
- Over the last 10 years alone, 850 million packages of OTC antihistamines for adults alone have been sold in the United States for these purposes.[2]

OTC antihistamines have been thoroughly studied for their safety, and where appropriate, they bear specific warnings related to important side effects. For example, different first-generation antihistamines may be associated with different levels of drowsiness. As a result, the OTC Review panels concluded that different warnings should appear on certain classes of antihistamines. Specifically:

"For products containing brompheniramine maleate, chlorcyclizine hydrochloride,

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[1] Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Antihistamine Drug Products; Final Rule (*Federal Register* 57: 58356-76, 1992); Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use; Final Monograph; Final Rule [54 F.R. 6814-27 (2/14/89)]; Antiemetic Drug Products for Over-the-Counter Human Use; Final Monograph; Final Rule (*Federal Register* 52: 15886-93, 1987)

[2] NOTE: Rx usage is not included in this figure of 850 million packages of OTC antihistamines for adults alone sold over the 10-year period from January 1, 1991 through December 31, 2000.

chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride: 'May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery.'" [emphasis added)

"For products containing diphenhydramine citrate or diphenhydramine hydrochloride: 'May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery.'" [emphasis added]
[*Federal Register* 57: 58374-5]

III. Post-marketing Safety Profile of OTC Antihistamines: 1991-2000

While the National Transportation Safety Board (NTSB) has asked about transportation-related accidents reportedly associated with OTC antihistamines, a thorough review of the available data from FDA's adverse experience reporting (AER) surveillance system shows no signal of concern.

OTC and Rx antihistamines included in the analysis of reports to FDA's AER surveillance system included the following drugs:

Brompheniramine	Diphenhydramine
Dexbrompheniramine	Doxylamine
Chlorpheniramine	Meclizine
Cyclizine	Phenindamine
Dexchlorpheniramine	Pyrilamine
Dimenhydrinate	Triprolidine

For these drugs over the last 10 years (01/01/91-12/31/00), there have been four or fewer serious or non-serious[3] AERs per year where the description of the event included the term "accident." For persons 16 years or older (i.e., driving age), there were a total of 23 cases over 10 years in FDA's AER system, on a base of 850 million packages of OTC antihistamines for adults alone sold in the United States over this period[4] (Attachment A). The term "accident" includes all types of accidents, from falls unrelated to transportation per se to accidents relating to cars, planes, boats, etc., and includes over 90 event-related "accident" terms such as fall, limb injury, etc.

[3] (as defined by MedWatch)
[4] NOTE: While Rx antihistamines are included in the AER analysis, Rx usage is not included in this estimate of 850 million packages of OTC antihistamines for adults alone sold over the ten- year period of the study.

Hence, while a rate of occurrence cannot be precisely determined from these data, the data are nevertheless supportive of the fact that there is no unexpected signal for concern in FDA's AER database related to accidents associated with reported OTC or Rx antihistamine use.

More specifically:

- Over the last 10 years (01/01/91-12/31/00), of the 23 adverse events (AEs) which were identified as "serious" in persons ≥ 16 years of age and which included the term "accident": (Attachment B)
  - 18 reported antihistamines as the primary suspect drug
  - 5 reported antihistamines as the secondary suspect drug

- Of the 18 AERs with antihistamines as the primary suspect drug in the FDA AER database over the last 10 years (01/01/91-12/31/00) (see Attachment B):

  - For single OTC cold/flu antihistamine-containing product exposures, there are:
    - 1 grand mal seizure with spontaneous bone fracture with an accident term
    - 2 overdose, accidental injury (one as a consumer report)
    - 1 accident, injury, drug toxicity, with no other discerning information (consumer report)

  - For single OTC sleep-aid product exposures, there were:
    - 1 non-accidental overdose with toxicity likely associated with the non-antihistamine ingredient in the OTC combination product
    - 1 completed suicide; non-accidental overdose; laceration (consumer report)
    - 1 accidental injury with no other discerning information (consumer report)

  - For single OTC or Rx antiemetic product exposures
    - 2 accidental injury: one with arrhythmia/palpitations; one with psychotic depression, dizziness
    - 1 fall associated with convulsions, apathy, blindness, fatigue, nausea, vertigo, weakness

  - For multiple OTC product exposures, there is:
    - 1 subarachnoid hemorrhage, altered neurotransmitter levels, hypertension (two OTC products)

  - For multiple OTC/Rx product exposures (2-6 OTC plus Rx products), there were:
    - 1 subarachnoid hemorrhage, headache, tremor, vomiting
    - 1 cerebral infarction with chest tightness, hemiparesis, hemiplegia and other associated events
    - 1 overdose, accidental injury
    - 2 falls (one associated with postural hypotension; the other with amnesia, confusion, unequal pupils, tachycardia, tremor, hypersecretion)
    - 1 non-accidental overdose, with a fall (consumer report)

- For multiple product exposure with no specification as to the Rx or OTC status of the primary suspect antihistamine, there was:
  - 1 accidental injury with no other discerning information (consumer report)

Hence, of the 18 AERs (i.e., that were serious with an "accident" term) identified from 1991 to 2000 where antihistamines were listed as the primary suspect drug, there are potentially plausible explanations for at least 7 of the AER cases, unrelated to the issue of drowsiness or performance effects of oral antihistamines on vehicular transportation/machinery when used by persons ≥ 16 years of age at recommended doses, including: 2 subarachnoid hemorrhages; 1 cerebral infarction; and 4 falls. For the remaining 11 AERs reported over the 10-year period of the study, information is insufficient to assign with any degree of confidence drug-accident causality in the context of use of vehicular transportation or machinery.

- Of the 5 AERs with antihistamines as the secondary suspect drug in the FDA AER database over the last 10 years (01/01/91-12/31/00; not shown in a table):
  - For multiple OTC drug product exposures, there are:
    - 1 Stevens-Johnson Syndrome, which appear to be listed twice
  - For multiple OTC and Rx product exposures, there are:
    - 2 suicide attempts with the Rx drug as the primary suspect drug
    - 1 convulsions with the Rx drug as the primary suspect drug
    - 1 AER with 58 event terms relating to widespread organ system failure and 67 drug terms, with a Rx drug as the primary suspect drug
  - For these 5 AERs, there are no listed transportation-related event terms.

- Finally, a search of FDA's AER database for AERs associated with serious and non-serious outcomes and the term "traffic accidents" identified 3 cases over the past 10 years (01/01/91-12/31/00) where an antihistamine-containing product was reported as the primary or secondary suspect drug (Attachment C):

  - 1 multiple Rx drug exposures (Rx antihistamine reported as secondary suspect drug; non-serious case);
  - 2 suicide attempts, one related to an OTC cold/flu combination product (antihistamine combination product listed as primary suspect; non-serious case) and one related to multiple OTC and Rx exposures (antihistamine sleep-aid product listed as secondary suspect product; serious case)
  - Note: there were 5 cases where antihistamines were listed as concomitant drugs, but not as primary or secondary suspect drugs (Attachment B). These 5 cases involved antiemetic antihistamines typically in multiple drug exposures involving prescription drugs.

- Given that 850 million packages of OTC antihistamines for adults alone have been sold over the 10-year span of this AER survey (and a much greater number if Rx sales are considered), the safety profile of first-generation antihistamines is excellent in

relation to potential transportation-related AERs reported through FDA's adverse event monitoring system.

IV. Overview of Selected Published Studies on Antihistamines

Support of the AER profile of antihistamines comes from several larger-scale epidemiologic studies that have attempted prospective assessments of the association between medicines (and illicit drugs) and highway crashes or fatal aviation accidents or that have reviewed the literature. In general, these studies demonstrate a low involvement, if any, between OTC medication use and fatal highway crashes.

A. Studies on Driving

1. Selected Studies Relating to Antihistamines

The National Highway Traffic Safety Administration (NHTSA) reported on alcohol and drug concentrations in operators of cars, trucks and motorcycles who died within 4 hours of their crash. [5] Forty-three drugs and alcohol were assayed in blood specimens collected from 1882 drivers from seven States over 14 months from 1990 to 1991. Drug assays included both drugs of abuse and certain medicinal drug ingredients. No distinction was made with respect to whether the two antihistamines assessed in the study (i.e., diphenhydramine and chlorpheniramine) were used as Rx or OTC products. In the study:

- Alcohol was found in 51.5% of specimens, and other drugs in 17.8%, with the most prevalent drugs being cannabis (6.7%), cocaine (5.3%), benzodiazepine tranquilizers (2.9%) and amphetamines (1.9%).
- As reported by NHTSA, "medicinal drugs were noteworthy for their low frequencies." The prevalence rate reported for antihistamines was 0.6% (n=13 or 1,882 drivers).
- NHTSA also observed, "Multiple drug use not involving alcohol was rare...a drug combination not involving alcohol was found in only 1.3 percent of the drivers. In these few cases, abuse drugs and benzodiazepines were again prominent."
    - In 6 cases, only the antihistamine was found in the system; in 7 cases, either alcohol with an antihistamine or alcohol with antihistamines and one or more other drugs were found in the system. Responsibility analysis showed no significant difference from drug-free drivers, although NHTSA noted the small numbers may have contributed to this finding.
- NHTSA concluded, "This and other studies have found that there are relatively few drugs which have prevalence large enough to present a highway safety problem. These were mainly drugs of abuse."

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[5] Terhune, K. W. et al.: The incidence and role of drugs in fatally injured drivers. U.S. Department of Transportation, National Highway Traffic Safety Administration Report No.: DOT HS 808 065, October 30, 1992.

- NHTSA also cautioned, "Caution must also be exercised in interpreting analytical results as they relate to the physiological effects of drugs on drivers in motor-vehicle-related deaths. Predicting the effects of drugs on driving skills is a nebulous exercise in the living subject; difficulties are compounded when attempts to make such predictions are based on postmortem measurements."

Research, conducted by Turnbridge et al. (2000)[6] as part of the CERTIFIED European Union research project, prioritized drugs (both licit and illicit) and medications in terms of their traffic safety risk potential. Results from 69 epidemiological studies were reviewed. Researchers considered the following 3 factors in developing the priority assignments: (1) research evidence of impairment effects; (2) estimates of exposure within the driving population; and (3) association with accident causation. Priority assignments were subsequently used to identify and drive research studies. Three levels of priority (high, medium and low) were assigned to index the safety risk potential of various medications and drugs.

Turnbridge et al. found that " very few epidemiological studies have found antihistamines in a significant percentage of the driving population." Relative risk for antihistamines ranged from 0.7 to 1.8 across studies. A relative risk of 1 would indicate that antihistamine-related crashes are not over- or under-represented. Generally, a relative risk equal to or greater than 2 indicates a significant or meaningful level of over-involvement. Given the reported relative risks, antihistamines were assigned a low priority. In contrast, alcohol and benzodiazepines were given high priority. The researchers stressed that this effort represents a "reasonable first approximation of relative accident risk."

Leveille et al.[7] conducted a population-based matched case-control study of 223 older drivers who were enrollees of a large Seattle-based health maintenance organization and 447 controls. The drivers were involved in injurious crashes during 1987 and 1988. Drug exposure was assessed as having had a prescription filled within the last 60 days for the drug of concern (cyclic antidepressants, opiods, benzodiazepines and sedating antihistamines). For sedating antihistamines, diphenhydramine accounted for 80% of the exposure. The investigators concluded:

> "The results indicate that antidepressants and opiod analgesics place older adults at increased risk for injurious motor vehicle collisions. Benzodiazepines and sedating

[6] Turnbridge, R., Clark, A., Ward, N., Dye, L., and Berghaus, G.: Prioritizing drugs and medicines for development of roadside impairment testing. CERTIFIED-DR1, University of Leeds (Work funded by the European Commission), 2000.

[7] Leveille, S. G. et al.: Psychoactive medications and injurious motor vehicle collisions involving older drivers. Epidemiology 5: 591-598, 1994.

antihistamines appear to have little effect on risk."

2. Comments on Extrapolating from Simulators to In-use Operation of Vehicles and Machinery

There are two basic challenges to using driving performance measures to index safety and impairment: (a) predicting how performance will translate into actual safety outcomes (i.e., crashes), and (b) understanding or selecting measures that are sensitive to the type of impairment under study. There is no simple relationship between driving performance and crashes, and drivers can selectively allocate attentional resources to primary or secondary tasks, making performance decrements in one area difficult to interpret or generalize due to trade-offs in another (e.g., better steering control, but more variability in speed). Also, driving measures are not sufficiently diagnostic to differentiate one category of impairment (alcohol) from another (fatigue).[8]

Simulators are intended to mimic actual driving situations and can provide a safe means for implementing controlled and repeatable studies. From an ethical standpoint, high-risk studies like those looking at impacts of alcohol or drugs on driving performance must be conducted in a controlled and safe environment. Simulator studies are particularly relevant and appropriate for this type of research since they provide high degrees of control in a low-risk environment. Simulator studies have the primary advantage of being able to precisely control and repeat driving experiences and conditions under which testing is performed (day/night, wet road conditions, rain, fog, etc.). They also allow for precise vehicle control and driving performance measurement. Nevertheless, because there is no standard protocol for driving scenarios or measures executed in simulator research, studies using simulators can vary substantially in these regards.

It is important to understand that driving simulators are primarily used to measure driving performance and not driving behavior. Simulators assess what drivers may be capable of doing in a controlled environment but do not necessarily measure what drivers actually do. Simulators also vary widely with respect to the degree to which they faithfully duplicate the physical and functional aspects associated with real driving environments, such as motion, vehicle dynamics, external environments (signs, buildings, traffic volume, pedestrians, etc.), as well as their physical layout (size of visual field, presence of vehicle cab, mirrors, etc.). As a result, cues in simulated driving environments may be substantially different than those encountered in real-world driving environments, and artifacts can be introduced into these environments that

[8] Fairclough, S.: Monitoring driver fatigue via driver performance. In: Noy, I. (Ed.) *Ergonomics and Safety of Intelligent Driver Interfaces*. Erlbaum, Mahweh, NJ. Pp. 363-379.

may not reflect actual behavior or performance. For example, speed and depth cues in simulated environments may be more subtle or difficult to accurately sense, making it harder for drivers to gauge acceleration, deceleration, braking performance, and distance to vehicles and objects. Sign readability has long been a problem in simulated environments. These differences can sometime influence results, and as a general rule tend to restrict or limit the ability to generalize results to the real world. This is perhaps the single biggest limiting factor with simulator research – the ability to generalize to real-world environments. (Of course, this same restriction can apply to test-track or on-road research as well). Simulator sickness can also be a problem, particularly with older individuals who may be more susceptible to its effects (this can be a problem if a representative sample of the driving population is desired).

There is no simple relationship between driving performance and crashes, and drivers can selectively allocate attentional resources to primary or secondary tasks, making performance decrements in one area difficult to interpret or generalize due to trade-offs in another (e.g., better steering control, but more variability in speed). A further difficulty in extrapolating from the controlled simulator environment to real-world situations stems from choices medication users may make in dealing with their condition and medication use. For example, studies indicate that consumers read the OTC label before using the product the first time.[9] Therefore, consumers suffering from illness and using medications may choose not to drive. There is substantial individual variability in susceptibility to the drowsiness effect of OTC antihistamines, which is dose-dependent. A consumer may self-select a lower dose of antihistamine, choose to use the antihistamine at bedtime, as directed for OTC sleep aids, or choose not to use an antihistamine. Further, consumers may undertake avoidance strategies when driving and experiencing drowsiness (e.g., pulling to the side of the road, opening the window, changing drivers, raising the volume of the radio, slowing driving speed).

In summary, the limitations of the highly controlled simulator environment, the potential compensatory responses to drowsiness, and adequate product labeling on OTC drug products all lead to question the ability to extrapolate from performance studies to demonstrate that a traffic safety problem exists in the real world in relation to antihistamine or other OTC drug use. There is no simple relationship between lab/test-track/controlled studies and actual performance in the real world, and it should not be assumed that findings in controlled settings will necessarily manifest themselves in terms of increased crash risk or estimates of crashes. A wide variety of compensatory mechanisms may take effect.

[9] Heller I, Heller II, and Roper studies, sponsored by CHPA.

B. Comments on FAA's Report: Prevalence of Drugs and Alcohol in Fatal Civil Aviation Accidents 1994 - 1998

In June 2000, the Civil Aeromedical Institute (CAMI) of the Federal Aviation Administration (FAA) issued a report entitled, "Prevalence of Drugs and Alcohol in Fatal Civil Aviation Accidents Between 1994 and 1998." Two of its major conclusions are misleading, specifically: (a) "[O]ver-the-counter medicines are the most frequently found drugs in fatal aviation accidents and many of these drugs, or the medical conditions for which they are being used, could impair a pilot's ability to safely fly an aircraft" [emphasis added]; and (b) "[O]ver-the-counter (OTC) drugs were found in 301 (18%) of the pilots analyzed which constitutes an increase of 37% from the OTC drugs detected between 1989 to 1993."

The first of FAA's conclusions relating to OTC medicine use is not justified because of methodological limitations of the study, which:

- Did not permit identification of actual OTC or Rx product use; the study only identified drug ingredients from postmortem assays of tissue samples;
- Did not accurately distinguish between the Rx or OTC status of drug ingredients found in the postmortem samples, due to use of an outdated system for categorizing drugs as Rx or OTC[10] and as stated the inability to determine whether a pilot actually used an Rx or OTC product.

Hence, it is inaccurate to say that OTCs are the most frequently found drugs in aviation accidents. Further, even if this were the case, such a statement implies that all OTC drugs have an impact on performance, when this is not the case. Indeed, for example, by improving symptoms such as a tension headache with an OTC analgesic, any performance decrement from the condition might be ameliorated by the medicine.

The second conclusion that there was an increase in OTCs detected in the 1994 to 1999 cohort vs. the 1989 to1993 cohort is misleading. From the principal study investigator, we understand that from 1990 to1992 substantial changes were undertaken in the analytical capabilities of the forensic lab. Over the 1990-92 period the lab increased its screening capabilities by switching from lower sensitivity detectors to gas chromatography-mass spectrometry and then adding in 1992 high pressure liquid chromatography. Hence, we understand that care should be taken in drawing conclusions about trends in the data from 1989 to1993. While the study concludes that there was a 37% increase in OTC-associated fatal aviation accidents from the 1989 to1993 cohort to the 1994 to1999 cohort, the apparent increase from 207 cases to 301 cases may be an

[10] Note: a number of the ingredients listed in the FAA report were switched to OTC status but were identified as OTC, and others were identified as OTC, when they also had (during the study) and still have Rx uses. For example, certain ingredients that are OTC are also Rx in combination with a scheduled drug or another Rx ingredient (e.g., acetaminophen plus codeine; certain cough/cold combination products containing antihistamines). Thus, based on Table 3 in the FAA study, it is impossible to determine an accurate listing of OTC product use by the deceased pilots, and therefore the Table is misleading, except as a listing of all ingredients found by the forensic lab.

artifact unrelated to increased OTC usage by pilots. By 1993, the reported rate of OTC usage (notwithstanding the problems stated above with ingredient and product classification, but assuming a consistency to inaccurate identification) was essentially leveling off to the current annual rate. Therefore, it is inaccurate to suggest that OTC usage by pilots is higher in the second 5-year cohort than that first 5-year cohort.

In summary, the FAA study is of limited usefulness in defining the scope and nature of pilot use of OTC medicines, and therefore represents very limited support of any further public health interventions targeted at, for example, OTC antihistamine-containing product labeling. The FAA study report itself makes no causal association between use of antihistamines and fatal aviation accidents.

As explained below, FDA has already mandated specific antihistamine-related drowsiness warnings for OTC drug products, as well as situation-specific directions of use for night-time sleep aids (e.g., take before going to bed). Most recently, FDA has initiated new labeling for OTC drug products that makes the current warnings and directions for use even more prominent, readily available and consistently visible. Hence, efforts should be directed at the need for an enhanced emphasis on education to build further awareness among consumers and special operator groups about the need to "read and heed the label."

V. OTC Drug Labeling

A. OTC "Drug Facts" Labeling for OTC Antihistamines

Recently, FDA has promulgated the "OTC label rule," which specifies format and content changes to the OTC label to make them even more consumer friendly.[11] The "OTC label rule" revised the required OTC label information from paragraph form to outline form, creating more white space, grouping like information, and creating a logical flow to the warnings section. For OTC antihistamines, the drowsiness warning was re-formatted within a special "Drug Facts" box on the label.

For example, for the ethanolamine class of OTC antihistamines (see Attachment E):

When using this product

- marked drowsiness may occur
- alcohol, sedatives, and tranquilizers may increase drowsiness
- avoid alcoholic drinks
- use caution when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

[11] Over-the-Counter Human Drugs; Labeling Requirements; Final Rule, *Federal Register* 64:13254-303, 1999.

This new labeling makes the drowsiness warning more prominent and consistently placed (compare "before" and "after" "Drug Facts" labeling in Attachments C and D).

Most of the AERs collected by FDA on antihistamines (as low in number as they were), were from products bearing the "old format" label, not the new "Drug Facts" label. Since the data generated from the NHTSA, Leveille et al. and FAA studies were also over a time period before institution of the "Drug Facts" label requirements, the impact of the new format has not been fully realized.

Most OTC antihistamine-containing products marketed by CHPA members are already in the "Drug Facts" format, and all will be in this format prior to the applicable May 2002 implementation date. As much as the former label warnings did provide consumers with adequate warnings, the new label format will be even more accessible to consumers.

B. Directions for Use

In addition, to the "Drug Facts" labeling which makes warnings even more prominent, OTC labeling for antihistamines provides two additional aspects related to safe product use. First, the directions for use of OTC antihistamine-containing sleep aids and analgesic-sleep aid combination products stipulate that the products should be taken at bedtime. [12]

Second, the section on directions for use of antihistamine-containing allergy medicines provides a dose range that allows consumers flexibility in the amount of the medicine they take. For diphenhydramine, for example, a dosage range of 25milligrams (mg) to 50 mg per use is stipulated.[13] The OTC Panel concluded that drowsiness with diphenhydramine varies depending on dose, with the lower dose reportedly associated with drowsiness in about 10% or less of individuals. A number of manufacturers include the 25 mg dosage in their combination allergy products. Thus, consumers taking these OTC antihistamines have the option to take one or two tablets, in the context of the other information in the "Drug Facts" label cautioning them about marked drowsiness and their experience with the medicine.

VI. The Question of Pictograms and Symbols (or Icons)

We understand that NTSB has an interest in discussing the potential use of a special warning mechanism for drugs that are associated with drowsiness and performance effects, such as pictograms or symbols (or icons). Both CHPA and FDA

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[12] Nighttime Sleep-Aid DrugProducts for Over-the-Counter Human Use; Final Monograph; Final Rule, *Federal Register* 54: 6827, 1989.

[13] Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Antihistamine Drug Products; Final Rule, *Federal Register* 57: 58374, 1992.

have examined this issue as it pertains to OTC drug labeling, finding on close examination that there are a number of compelling reasons why pictograms or symbols are not workable in the OTC self-care setting.

From a "benefit" standpoint, pictograms and symbols have been suggested as solutions to conveying information on drug labels to individuals with lower/no literacy skills and to helping those individuals who choose not to read labels to understand important information on the label.

These putative benefits are, however, questionable at best, for the following reasons:

a. Pictograms and symbols are unproven as a benefit in any in-use situation for OTC labeling.

b. As important as it is to encourage individuals with lower literacy skills to learn to read (as is promoted today by a large number of local educational programs), such individuals are likely to have, as a practical matter, the same problems learning the language of pictograms as they would the English language – with the net result that pictograms, given their other limitations (see below), are not even comparable representations of words in the context of OTC labeling. Symbols are even less representative.

c. No data show that the smaller percentage of individuals who report they do not read OTC labels (note: the vast majority say they do; see Heller, 1983, 1992; Roper, 2001) would be more likely or even as likely to read (and correctly interpret) pictograms or symbols.

d. Given the large amount of information on many OTC labels (e.g., a four-ingredient cough/cold combination), there is a fundamental question as to which information would be chosen for representation with a pictogram or icon (see also below). With label space extremely limited for most package sizes, not all the essential information could possibly be conveyed via pictograms or symbols on the label. Thus, if pictograms or symbols are expected as either the primary aid for illiterate individuals or those who do not read labels, the fact that only part of the label is represented by pictograms or symbols would mean a system has been created that encourages partial information transfer. Such a situation would potentially mean more important warnings without pictogramatic emphasis would become de facto less prominent (see also this section below pertaining to the medical perspective)

e. The emphasis for pictograms and symbols has been placed largely on drug label warnings and directions for use. As a practical matter, if a person is illiterate, how would he or she know which products to chose for a particular condition in order to receive the pictogramatic information?

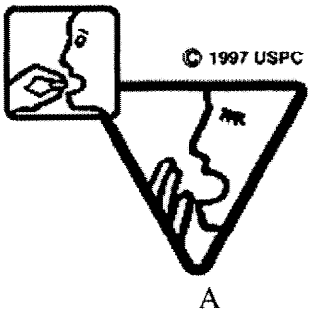
From a "risk" standpoint, pictograms and symbols have a number of limitations that outweigh any possible benefit, thus leading to the conclusion that pictograms should not be a required part of OTC labeling for the following reasons:

a. From a medical standpoint, the potential for partial and/ or incorrect information transfer is of great concern.

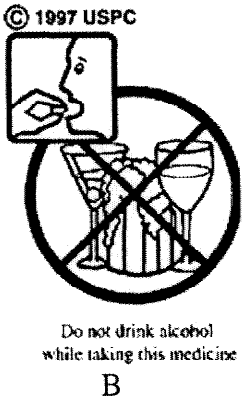
As noted under "d." above, use of pictograms or symbols to represent some warnings, but not others, could imply other warnings are of lesser importance. Given the available data, there seems to be no justification to create the potential situation for a cough/cold combination product where, for example, statements about drug-drug/condition interactions, relative contraindications against use during pregnancy/nursing, or keeping the product out of the reach of children might be interpreted as less important than the use caution about driving a motor vehicle.

In addition, pictograms have the potential to be interpreted differently by the wide variety of potential readers who have different social and education backgrounds raises important questions in terms of safe use of OTC medicines.

For example, the two pictograms from the United States Pharmacopeia shown below can each be interpreted in vastly different ways, which – depending on interpretation – could result in unintended uses of a drug product. In the first example (Figure A), the interpretation might be "makes you drowsy," "take when sleepy," "take at bedtime," "take for a cough," or simply the next frame of the cartoon showing that the drug should be taken by mouth.



A



B

Even the international "no" sign (i.e., a diagonal line drawn through a circle) would result in similar difficulties and incorrect interpretations. This symbol is often interpreted as an absolute negative with respect to any picture representation appearing to be "struck out" by the diagonal line. The "No Parking" sign used in traffic control is a daily re-enforcement of this interpretation. While on the surface this might be considered an advantage, the pictorial representation beneath the diagonal line can be translated differently resulting in different interpretations of the intended negative. For example in Figure B, the

interpretations might be "don't drink alcohol," "don't drink wine," or – in the case of test subjects who do not imbibe – "don't drink anything – take the medicine without liquid."

b. From a liability standpoint, pictograms and symbols create an additional set of limitations that are not outweighed by any potential benefits.

Not all label information can be represented by pictograms and symbols on OTC labels. For example, a typical cough/cold label contains 16 different conditions for which product use should be avoided unless otherwise directed by a physician. As a practical matter due to space limitations and slack-fill considerations, not all of these conditions could be represented in pictograms on the OTC label. Which would be chosen for representation? From a liability standpoint, which conditions would not be chosen for representation? For that matter, it is unlikely from a liability standpoint that pictograms symbols could be used as partial representations of certain of the label information.

Beyond the limited space consideration and the choice of which, if not all, information should be represented by pictograms or symbols, there is the additional concern that whatever information is represented by pictograms and symbols would be subject to misinterpretation, as discussed above. Such misinterpretations would likely occur and this has been shown in the published literature.[14] With no demonstrable public health benefit for pictograms or symbols, the attendant public health and liability concerns outweigh the limited usefulness.

c. From a scientific standpoint, pictograms and symbols can also be misrepresentations of the available data.

For example, if an antihistamine-containing anti-allergy product contains a pictogram of a yawning face, the pictogram would be falsely interpreted if the individual thought it meant that *all* users of the medicines would become drowsy, since not everyone is susceptible to the drowsiness effects of antihistamines. A pictogram cannot give a graded interpretation, such as "*may* cause drowsiness," which is the scientifically appropriate warning. A symbol would be interpreted similarly. Indeed, if a consumer interprets the pictogram as a perceived "absolute" side effect, would he or she doubt the efficacy (or overdose themselves) if the side effect does not occur?

Thus, because pictograms and symbols imply "all or none" situations, the conditional accuracy of warnings which is denoted through the use of such words as "may" is lost. Pictograms and symbols thereby become scientifically inaccurate and possibly misleading representations of OTC label information.

[14] E.g.: Hanson, C., and A. Hartzema: Evaluating pictograms as an aid for counseling elderly and low-literate patients. J. Pharm. Mark. Man. 9(3): 41-54, 1995.

d. From a label readability standpoint, the use of pictograms and symbols invades the available label space for more complete and meaningful written directions of use, warnings, drug interaction precautions, etc. While type size is but one factor in label readability,[15] it is an important factor, so that any additional space-filling label feature that would work against type size should be very carefully considered for demonstrable benefits before it is made a mandatory part of labeling. For pictograms or symbols, there is sufficient question about their usefulness to conclude that they should not be a mandatory part of OTC labeling.

In fact, it is important for consumers to read the entire label. To this end, the OTC label is organized in "chunks" of information[16] in sequence from absolute contraindications to relative contraindications and in-use precautions, as a means to help the logical transfer of information and, thereby, aid information processing by the consumer. A pictogram or icon within the "Warning" section would potentially interrupt the logical flow of information by drawing the consumer's eye to the pictogram or icon out of sequence relative to the presentation of label information. This could be potentially counter-productive to the medical need for full reading of the label. Hence, without data to demonstrate that symbols or pictograms actually provide a benefit for the situation noted by NTSB, there is little basis for support for their mandatory use.

At the November 14-15, 2001 FDA/ NTSB hearing on this matter, there was little support given to the use of pictograms on OTC labeling. Since the transcript of the FDA/NTSB meeting was not available when the public comment period closed, we have not highlighted specific comments by experts speaking at the November 14-15 meeting.

We understand that some time ago the Nordic Council on Medicines initiated a project to place a red triangle on medicine packages as a "traffic warning." At that time the European Union had not initiated its program on medicinal label content and format that is similar in many respects to the recent FDA initiated "Drug Facts" labeling. We understand that the Swedish Lakemedelsverket (Medical Products Agency) has asked the national trade association if the red triangle can be dropped from drug labeling, based on the availability of full labeling on antihistamines relating to drowsiness. Anecdotally we are told some patients/consumers think the red triangle is a pregnancy warning, raising concerns about consumer confusion. Hence, where there has been experience with an icon on product labeling, authorities do not appear convinced the icon should be a sustained product feature.

During the November 14-15, 2001 FDA/NTSB hearing on this matter, there was little support given for the use of the red triangle. Again, as mentioned above, since the transcript of the meeting was not available at the time of this submission, specific comments in support of this observation are not included here.

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[15] CHPA Label Readability Guidelines.
[16] Described as "chunking" by label readability experts.

In summary, the benefits of pictograms or symbols for OTC labeling have not been demonstrated in actual use situations. There remain substantial, and insurmountable, questions as to their usefulness on OTC labeling from medical, scientific and legal perspectives. The variety of interpretations/misinterpretations that might arise from the use of pictograms or symbols on OTC labels is their fundamental failure for self-care situations with OTCs. For all these reasons, pictograms or symbols would represent an inappropriate regulatory approach for OTC medicines. Furthermore, with "Drug Facts" labeling the drowsiness warning on antihistamines is more prominent and consistently placed (as noted above).

VII. Education: "Read the Label"

As presented above, we see no clear signal for concern from FDA's post-marketing AER surveillance system, and OTC antihistamines are appropriately labeled with clear, prominent consumer-friendly warnings about drowsiness. Hence, efforts to address responsible OTC medication use should be aimed at education, as a means to build awareness of the need to read the label and heed the directions of use and warnings.

CHPA has had a long-standing effort to promote the message, "read the [OTC] label" and plans to continue these efforts. Since FDA first initiated its OTC Review in the early 1970s, CHPA has been extremely active in educating consumers about the importance of reading the labels on all over-the-counter medicine products. The Association's first consumer information brochure incorporating that theme, *Medicine Labels and You*, was printed in 1972 -- the same year the OTC Review began. Since that time, CHPA has developed and distributed widely a number of additional educational pieces that were either produced solely by the Association or in partnership with an ally organization, such as:

- U.S. Food and Drug Administration
- The National Council on the Aging
- National Council of Negro Women
- The National Hispanic Council on Aging
- National Women's Health Resource Center
- American Optometric Association
- National Council of La Raza
- United Seniors Health Cooperative
- Older Women's League
- Partnership for a Drug Free America
- Wellness Councils of America
- YWCA of the U.S.A.

The most recent example of CHPA's continued efforts to spread the word on reading the label is an updated version of a brochure entitled *Over-the-Counter Medicines: What's Right for You?* CHPA was successful in partnering with FDA again on this popular brochure and recently printed a total of 150,000 copies of *"What's Right for You"* for distribution. To date, CHPA has disseminated just under six and one-half million consumer information brochures that urge consumers to "read the label."

CHPA brochures typically highlight selected portions of important label information, including warnings pertaining to antihistamines and drowsiness. For example, the current CHPA partnership with the Older Women's League places emphasis on "drowsiness-motor vehicle/machinery" warnings for antihistamine-containing products. The current CHPA partnership with the Food and Drug Administration on the *"Medicine Works Best When You Read the Label"* brochure urges consumers to be on the alert for possible side effects, such as drowsiness.

In addition, The Council on Family Health (CFH) was created in 1966 by the makers of OTC medicines to distribute public education information on safe medicine use and other personal and home safety issues. In the years since, the Council has served as a clearinghouse of consumer-friendly information stressing the importance of reading and understanding over-the-counter medicine labels. To help communicate this important health-related information, CFH has partnered with a number of nonprofit and government entities, including:

- Food and Drug Administration
- Federal Bureau of Investigation
- Federal Consumer Information Center (FCIC) at Pueblo, Colorado
- American Medical Association
- English as a Second Language teachers
- National Association of Chain Drug Stores
- National Association of School Nurses, Inc.
- National Coalition of Hispanic Health and Human Services Organizations
- National Consumers League
- National Council of Negro Women
- National Council on La Raza
- National Council on the Aging, Inc. (NCOA)
- National Hispanic Council on Aging
- Pharmaceutical Research and Manufacturers of America
- Poison Prevention Week Council
- *Prevención*, Inc.

In its three-and-a-half decades of service to the community, CFH messages on the importance of reading medicine labels have been featured in every major U.S. newspaper, news magazine, and news outlet, including *Time Magazine*, the *Wall Street Journal*, the *New York Times*, *Los Angeles Times*, and the CBS Evening News. Over the past five years, the Council has averaged 193.96 million media impressions a year.[17] So far in 2001, the Council has earned 194 million media impressions.

Almost every CFH program in recent years has featured the cornerstone message: "Read the label." This message has been tailored to a number of audiences over the years, including general consumer audiences, older Americans, Spanish-speaking consumers, older Spanish-speaking consumers, parents, and English-as-a-second-

[17] 241.8 million in 2000; 204.0 million in 1999; 86.7 million in 1998; 192.8 million in 1997; 244.5 million in 1996

language speaking consumers. Printed publications for the Council include brochures, shelf-talkers, tips sheets, posters, etc. The Council has used all communications media to disseminate this important information broadly, including print, radio, and TV public service announcements (PSAs); editorial stories; press releases and media outreach; video news releases (VNRs); and the Internet. In fact, www.cfhinfo.org was selected for inclusion in the federal healthfinder® Web site.

In summary, CHPA and CFH have had long and successful histories of developing partnerships to promote the "Read the Label" message to consumers. These partnerships have focused on how to read the label, including the importance of such specific warnings as those relating to antihistamines and drowsiness. CHPA continues to be willing to explore additional joint efforts as a means to build awareness of the need not only to "read the label" and but also to follow directions for use and warnings.

VIII. Commentary on Drowsiness, Drowsy Driving and OTC Medication Use in the Context of "Drug Facts" Labeling and Public Education

Each year, approximately 100,000 crashes are attributed to drowsy driving.[18] This represents approximately 1.6% of the total 6.3 million police-reported crashes each year, including both passenger vehicles and commercial vehicles. Drowsy driving appears to be relatively more frequent and problematic in commercial vehicle populations, and, as a result, fatigue is one of the major concerns in trucking safety. This is primarily a result of increased number of miles driven. Although approximately 96% of drowsy driver crashes involved passenger vehicles (the remaining 3-4% for commercial vehicles), commercial drivers' risk of being involved in a fatigue-related crash is far greater than drivers of passenger vehicles. Expected involvement for trucks is 4.5 times greater than for passenger vehicles, again, primarily due to greater mileage driven and more frequent nighttime driving.

Drowsy driver crashes often take the form of Single Vehicle Roadway Departures (SVRD), and tend to occur on highways where most long-distance nighttime driving takes place.[19] Typically, drivers fall asleep at the wheel, or the driver's sleepiness leads to reduced performance and loss of attention. Fatalities from drowsy driving constitute approximately 3.6% of all fatal crashes each year. The strongest and most consistent factor influencing driver drowsiness/fatigue and alertness is time of day (crashes occur predominantly after midnight, with a secondary peak in the midafternoon). Nighttime and midafternoon peaks are consistent with human circadian rhythms.

Factors that influence drowsiness (irrespective of the situation) include, among others, sleep loss and sleep disorders, driving patterns, and consumption of alcohol, and use of medicines and illicit drugs. The leading cause of drowsiness in people without sleep disorders are sleep restrictions and sleep fragmentation.[20] While medication use may be considered a potential cause of drowsiness, the epidemiologic assessments

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[18] http://www-nrd.nhtsa.dot.gov/departments/nrd-01/summaries/its_11.html

[19] NCSDR/NHTSA Expert Panel on Driver Fatigue and Sleepiness: Drowsy driving and automobile crashes. http://www.nhtsa.dot.gov/people/injury/drowsy_driving1/drowsy.html

[20] Proceedings of a conference ATA in 1996

highlighted in this submission support the conclusion that OTC antihistamines are not a significant contributing factor to motor vehicle-related accidents. Reasons supporting this conclusion are:

- OTC products are appropriately labeled, and those with known drowsiness side effects (i.e., antihistamines) have labeling specifically targeted to motor vehicles and machinery use;
- The new "Drug Facts" labeling will add new prominence and more consistent placement of warnings than the "old" OTC label;
- Consumers report that they do read the label before using the product the first time;
- The OTC industry has had a long history of involvement in public education directed at "read the OTC label;"
- The 10-year post-marketing adverse reporting experience for Rx and OTC antihistamines shows no unexpected signal for concern;
- Drivers and machinery operators may use compensatory strategies to address drowsiness during driving or machinery operation.

As a result, CHPA sees no data to support further changes in OTC drug labeling. Emphasis on the importance of reading and heeding the OTC label is a public health tactic CHPA has long supported, and the Association is willing to explore additional joint efforts that might target this message even better.

IX. Conclusions

OTC antihistamines have a remarkable history of safe and effective use, when used according to label directions. This conclusion is supported by CHPA's analysis of FDA's AER database, in which 23 non-serious or serious AERs associated with antihistamines and an accident term were reported over a 10-year period, on a base of 850 million packages of OTC antihistamines for adults alone sold in the United States during the same period.

CHPA has a record of working well with FDA to continually improve OTC drug labels to help ensure consumer awareness and understanding.

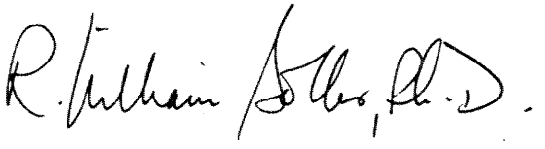
Pictograms and symbols are potentially confusing, rob scarce label space without a public health benefit to their use being demonstrated, and potentially could lead consumers to ignore more important warnings for their particular underlying condition. They are unproven in any use situation for OTC medicines.

The available data from FDA's adverse experience reporting system and the unproven nature of pictograms and symbols in an OTC setting provides no support for changes in OTC labels to bring further prominence to drowsiness warnings on OTC antihistamines, either by pictograms or other means.

CHPA believes it is important to maintain an ongoing program of consumer education on the importance of reading the label. Over the years, CHPA has partnered with many organizations, providing educational materials for distribution by these "message multiplier" groups. These groups include FDA, National Consumers League, among others. CHPA remains committed to continuing its efforts to inform consumers about the importance of reading the OTC label, and thereby informing them about proper and responsible use of OTC medicines.

Finally, since the transcript of the FDA/NTSB meeting of November 14-15, 2001, was not available at the time of this submission, specific points made by experts at the meeting are not included here. However, we intend to review the transcript and provide an addendum to this submission, in which specific aspects of the meeting are highlighted in support of the perspective and conclusions provided in this submission.

Respectfully submitted on behalf of the CHPA Antihistamine Task Group by:



R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology
Consumer Healthcare Products Association

Attachments:
- A Chart of AE Reports with an "Accident" Term for Suspect Antihistamine (Serious and Non-Serious) by Year (01/01/91-12/31/00)
- B Summary Compilation of AERs Reported to FDA's AER Surveillance System. January 1, 1991 – December 31, 2000. "Serious" AERs in Persons ≥ 16 years of Age with the Term "Accident" in Any AER Field
- C Summary Compilation of AERs Reported to FDA's AER Surveillance System. January 1, 1991 – December 31, 2000. "Serious" AERs in Persons ≥ 16 years of Age with the Term "Accident" in Any AER Field. Antihistamines Listed as Primary or Secondary Suspect Drugs or Concomitant Drugs with Specific Report of "Road Traffic Accident"
- D Ethanolamine Labeling Example: Pre-"Drug Facts" Labeling
- E Ethanolamine Labeling Example: "Drug Facts" Labeling

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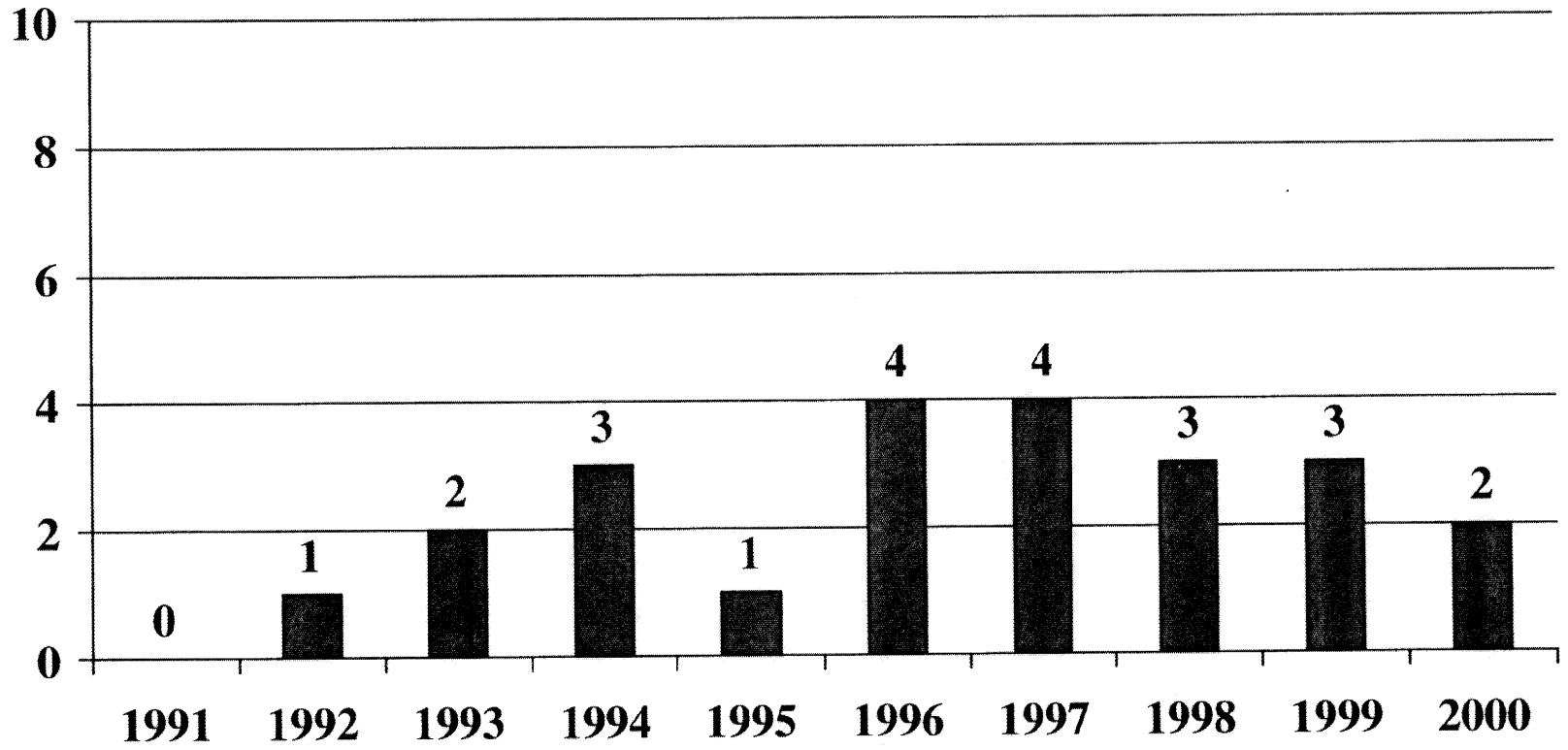
Total Adverse Experience Reports with an "Accident" Term for Persons ≥ 16 years of age



OTC and Rx AERs w/ AH as Primary Suspect (PS)	18
OTC and Rx AERs w/ AH as Secondary Suspect (SS)	5
OTC Packages Sold Over 10 years (1/1/91-12/31/00)/adults	~850 million

Attachment A

Attachment B

Summary Compilation of AERs Reported to FDA's AER Surveillance System
January 1, 1991 – December 31, 2000
"Serious" AERs in Persons ≥ 16 years of Age with the Term "Accident" in Any AER Field

Total "serious" in persons ≥ 16 years of age with the term "accident:"	23	
Serious AERs, ≥ 16 yo, "accident" term, Antihistamines as PRIMARY suspect drug	18	
For single OTC cold/flu antihistamine-containing product exposures		
▪ Grand mal seizure with spontaneous bone fracture with an accident term		1
▪ Overdose, accidental injury		2
▪ Accident, injury, drug toxicity, with no other discerning information		1
For single OTC sleep-aid product exposures		
▪ Non-accidental overdose with toxicity likely associated with the non-antihistamine ingredient in the OTC combination product		1
▪ Completed suicide; non-accidental overdose; laceration		1
▪ Accidental injury with no other discerning information		1
For single OTC or Rx antiemetic product exposures		
▪ Accidental injury: one with arrhythmia/palpitations; one with psychotic depression, dizziness		2
▪ Fall associated with convulsions, apathy, blindness, fatigue nausea, vertigo, weakness		1
For multiple OTC product exposures		
▪ Subarachnoid hemorrhage, other symptoms, no injury/accident term (2 OTC prodcts)		1
For multiple OTC/Rx product exposures (A range of 2-6 Rx products with an OTC)		
▪ Subarachnoid hemorrhage, other symptoms, no injury/accident term		1
▪ Cerebral infarction with chest tightness, hemiparesis, hemiplegia, fall, other events		1
▪ Overdose, accidental injury		1
▪ Falls (one associated with postural hypotension; another with amnesia, confusion, unequal pupils, tachycardia, tremor, hypersecretion; another with non-accidental overdose)		3
For multiple product exposure with no specification as to the Rx or OTC status of primary suspect antihistamine		
▪ Accidental injury with no other discerning information, reported by a consumer		1
Subtotal		18
Serious AERs, ≥ 16 yo,"accident" term, Antihistamines,SECONDARY suspect drug	5	
For Multiple OTC Drug Product Exposures		
▪ Corneal lesion, Stevens Johnson Syndrome (2 reports, same case)		1
For Multiple OTC and Rx Drug Products Exposures		
▪ Suicide attempts, non-accidental overdose among other injury-event terms		2
▪ Fall, convulsions, loss of consciousness		1
▪ Injury, congestive heart failure, chronic obstructive airways, hepatic cirrhosis, cor pulmonale, portal hypertension, renal failure, splenomegaly, among other event terms and listing of 61 concomitant drugs		1

NOTE: The term "accident" includes all types of accidents, from falls unrelated to transportation per se to accidents relating to cars, planes, boats, etc., and includes over 90 event-related terms such as fall, limb injury, etc.

Attachment C

Summary Compilation of AERs Reported to FDA's AER Surveillance System
January 1, 1991 – December 31, 2000
"Serious" AERs in Persons ≥ 16 years of Age with the Term "Accident" in Any AER Field

Antihistamines Listed as Primary or Secondary Suspect Drugs or Concomitant Drugs with Specific Report of "Road Traffic Accident"

Subtotal	5

Antihistamines listed as PRIMARY or SECONDARY suspect drugs with specific report of "Road Traffic Accident"	3
Non-Serious AER with Antihistamine as PRIMARY Suspect Drug (PS) ▪ OTC cough/cold product (PS): Road traffic accident, suicide attempt, drug abuse, sedation	1
Serious AER with Antihistamine as PRIMARY Suspect Drug ▪ None	0
Non-Serious AER with Antihistamine as SECONDARY Suspect Drug (SS) ▪ Rx cough/cold with codeine (SS): Road traffic accident, dizziness, confusion	1
Non-Serious AER with Antihistamine as SECONDARY Suspect Drug ▪ OTC Sleep Aid (SS): Road traffic accident, suicide attempt, nonaccidental overdose, hepatoxoicity [likely related to PS drug] and other event terms	1

Antihistamines listed as CONCOMITANT medications (C) with specific report of "Road Traffic Accident"	5
Serious ▪ All 5 cases listed antiemetic antihistamine as concomitant medications. All five cases were reportedly on multiple Rx medications and listed an Rx medication as the primary suspect drug. Multiple medication use ranged from 4-53 total concomitant medications. NOTE: the case with 53 total concomitant medications also listed an OTC antihistamine-containing allergy medicine and unidentified "OTC cold medication."	5

Attachment D

Ethanolamine Labeling Example Pre Drug Facts Labeling

INDICATIONS: Temporarily relieves runny nose and sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies.

DIRECTIONS: Follow dosage directions below, o ruse as directed by your doctor. Take every 4 to 6 hours. Do not take more than 6 tablets in 24 hours.

AGE	DOSAGE
Adults and children 12 years of age and over	1 tablet
children under 12 years of age	Consult a doctor

WARNINGS: May cause excitability especially in children. Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

KEEP THIS AND ALL DRUGS OUT THE REACH OF CHILDREN.

In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

ACTIVE INGREDIENT: Each tablet contains: Ethanolamine x mg. Also contains: (inactive ingredients are listed)

Store at 59°-77°in a dry place.

Protect from light.

Attachment E

Ethanolamine Labeling Example (Drug Facts Labeling)

Drug Facts

Active ingredient (in each tablet) ***Purpose***

Ethanolamine x mg.....Antihistamine

Uses

- temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
  - runny nose
  - sneezing
  - itchy, watery eyes
  - itching of the nose or throat

Warnings

Ask a doctor before use if you have

- glaucoma
- trouble urinating due to an enlarged prostate gland
- a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product

- marked drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- use caution when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- take every 4 to 6 hours
- do not take more than 6 tablets in 24 hours

adults and children 12 years of age and over	1 tablet
children under 12 years of age	Consult a doctor

Other information

- store at 59° to 77°F in a dry place
- protect from light

Inactive ingredients (inactive ingredients are listed)

Questions?

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emp# 85975 17DEC01

TRK# 8317 1740 3874 FORM 0215

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Form I.D. No. 0215

Recipient's Copy

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records.

Date 12/17/01 FedEx Tracking Number 831717403874

Sender's Name R William Soller, PhD Phone 202 429-9260

Company CONSUMER HEALTHCARE PROD ASSN

Address 1150 CONNECTICUT AVE STE 1200

Dept./Floor/Suite/Room

City WASHINGTON State DC ZIP 20036

2 Your Internal Billing Reference 602

3 To

Recipient's Name Dockets Management Phone 301 827-6560

Company Food & Drug Adm.

Address 5630 Fishers Lane Room 1061

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Dept./Floor/Suite/Room

City Rockville State MD ZIP 20852

8317 1740 3874

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4a Express Package Service *Packages up to 150 lbs.* Delivery commitment may be later in some areas.

- [X] FedEx Priority Overnight — Next business morning
- [ ] FedEx Standard Overnight — Next business afternoon
- [ ] FedEx First Overnight — Earliest next business morning delivery to select locations
- [ ] FedEx 2Day — Second business day
- [ ] FedEx Express Saver — Third business day
- [ ] NEW FedEx Extra Hours — Later drop-off with next business afternoon delivery for select locations

FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx 1Day Freight* — Next business day
- [ ] FedEx 2Day Freight — Second business day
- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation:

5 Packaging * Declared value limit $500

- [X] FedEx Envelope*
- [X] FedEx Pak* — Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- [ ] Other Pkg. — Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling Include FedEx address in Section 3.

- [ ] SATURDAY Delivery — Available only for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- [ ] HOLD Weekday at FedEx Location — Not available for FedEx First Overnight
- [ ] HOLD Saturday at FedEx Location — Available only for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

- [X] No
- [ ] Yes — As per attached Shipper's Declaration
- [ ] Yes — Shipper's Declaration not required
- [ ] Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg

Dangerous Goods (incl. Dry Ice) cannot be shipped in FedEx packaging or with FedEx Extra Hours service.

- [ ] Cargo Aircraft Only

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below.

- [X] Sender — Acct. No. in Section 1 will be billed.
- [ ] Recipient
- [ ] Third Party
- [ ] Credit Card
- [ ] Cash/Check
- [ ] Obtain Recip. Acct. No.

Total Packages	Total Weight	Total Charges
1		Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See the *FedEx Service Guide* for details.

8 Release Signature *Sign to authorize delivery without obtaining signature.*

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

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447