CHPA

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Re: Comments on Citizen's Petition #FDA-2013-P-1001/CP-1

In Citizen Petition FDA-2013-P-1001/CP-1, it was requested that the Commissioner of Food and Drugs add a warning to the labeling of all nonprescription drug products containing an ingredient with anticholinergic or histamine H_1 inverse agonist effects to indicate that products with these ingredients can cause a confusional state including impaired attention, disorientation, and decreased power of concentration. The Petitioners further suggested that these drugs, when administered along with other prescription and nonprescription drug products containing anticholinergic or histamine H_1 inverse agonist active ingredients, can result in an increased degree of impaired cognition leading to an acute confusional state or delirium, especially in older people who are more at risk for this effect than younger people.

Herein, the Consumer Healthcare Products Association (CHPA), the 133-year-old trade association representing U.S. manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements (chpa.org), provides our comments on the Citizen Petition, with particular regards to the impact on the class of first-generation antihistamine active ingredients marketed in non-prescription drug products under the OTC monographs (*e.g.*, Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic; Nighttime Sleep Aid). As an attachment to this letter, we also include a review of the evidence cited in the petition conducted by Howard Druce, MD, Clinical Professor of Medicine at Rutgers University.

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At a general level, we observe that the Citizen Petition lacked specificity and clarity in defining the scope of the recommended label changes. For example, it was unclear exactly what products would be expected to carry the proposed labeling (*e.g.*, which non-prescription drugs/ingredients). Although the Petitioners sometimes referred to antihistamine ingredients, the term "ingredient with anticholinergic or histamine H_1 inverse agonist effects" was frequently used, and may be associated with other drug classes.

Similarly, it was not clear whether the Petitioners' proposed warning should relate to use in the general population, or to use in specific subpopulations. For example, the Petitioners described that certain populations (*e.g.*, older adults) may be at a heightened risk. Results were cited from studies in potentially vulnerable individuals (*e.g.*, elderly adults, patients with dementia, Alzheimer's, Parkinson's Disease, or patients taking certain other drug products, etc.). Additionally, it was unclear which prescription or non-prescription products/ingredients containing anticholinergic or histamine H_1 inverse agonist active ingredients may be contraindicated.

The Petitioners described certain agents as causing a confusional state, including impaired attention, disorientation, and decreased power of concentration. In an OTC environment, these terms are potentially ambiguous and may represent symptoms that are of non-specific origin from a consumer point-of-view. Consumers may interchangeably use these terms to describe either the effectiveness or the side effects of some OTC products. For example, symptoms such as these may be attributed to the known and adequately labeled side effect of marked drowsiness, associated with some OTC first-generation antihistamine products. Alternatively, they may be associated with the sedative, sleep-inducing benefits of the same ingredients in sleep-aid products. Finally, the nature of these adverse effects were not well characterized: for example, what level and duration of exposure leads to increased incidence of adverse events; what is the prevalence and severity of the effects; are there pre-conditions or exacerbating conditions; and how does this relate to OTC labeled uses?

As a means of assessing the relevance of the cited support to the Petitioners request for a label change, CHPA requested Dr. Druce to provide an overview of the documents noted in the petition. As described more specifically in his report (attached to this letter), the evidence provided by the Petitioners is not supportive of their request to add a Warning. Both prospective controlled trials presented as support (Sunderland *et al.*, 1987; Pomara *et al.*, 2008) encompassed small patient populations (n=20-24), involved drug/dosing regimens with limited or no applicability to nonprescription regimens (intravenous administration; prescription drug) and included either subjects with dementia or with an underlying comorbidity imparting an increased risk for dementia (carriers of the APOε4 gene). We view neither of these studies as substantiating the proposed label change.

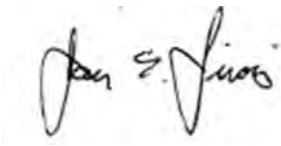
Two observational studies were cited as evidence (Ancelin *et al*., 2006; Landi *et al*., 2007). Although potentially supportive, both were both performed outside the United States and suffered from limitations, including lack of assessment of cognitive or behavioral impairment (Landi *et al*., 2007) and use of a novel, self-developed anticholinergic burden classification scale (Ancelin *et al*., 2006).

The Petitioners additionally noted that "case reports" suggested that confusion can result from anticholinergic effects of medications; however, no specific examples were provided. Finally, additional support was cited, but also suffered from a lack of relevance to a nonprescription use situation, due to analysis in a population with a comorbid condition (Perry *et al*., 2003), or lack of relevance to H_1 antihistamine products, or nonprescription drug/dosing regimens (Janowsky *et al*., 1972; Tune *et al*., 1992; Perry *et al*., 2003).

In summary, the Citizen Petition does not provide sufficient justification for the addition of a warning to nonprescription first-generation antihistamines regarding cognitive impairment. The majority of the evidence suffers from significant limitations including lack of applicability to antihistamine use in the OTC setting, use of patient populations with underlying comorbidities imparting an increased risk to cognitive deficits, and analysis of effects in patient populations of insufficient size. As such, we recommend that no additional warning language is required at this time.

CHPA members are committed to ensuring the safe and effective use of their marketed products and are willing to collaborate with the agency should they determine that additional efforts are necessary. Please feel free to contact me if you have any questions.

Sincerely,



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