Written Statement Submitted to Food and Drug Administration for the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee

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Background:

A variety of issues must be taken into account when considering requiring that a product be made available for "over-the-counter" (OTC) nonprescription use.

In this statement we wish to describe, briefly, concern about this process when applied to antihistamines. The issues that we raise herein can also be applied to other drug classes, but we focus on antihistamines, particularly on the differences between the so-called first- and second-generation agents.

In this statement, we also focus our comments on the use of driving studies, either using on-the-road driving performance or in a driving simulator, to examine impairment. In this statement, we do not consider other tests for impairment or other situations in which impairment might be problematic (e.g., in school or the workplace). We also do not consider other issues (including potential adverse events unrelated to impairment) that must be evaluated when considering making a drug available on a nonprescription basis.

We have recently authored a manuscript describing driving impairment in a driving simulator (1). We reported that subjects performed even more poorly, statistically, after receiving a first-generation antihistamine than they did after receiving alcohol. No such impairment was seen with the second-generation antihistamine that we studied as compared with placebo. This report agrees with the literature that already exists on antihistamines and driving performance (in lower-fidelity machines, using on-the-road driving experiments, and in other laboratory settings (2, 3, 4, 5)) that indicates that some antihistamines impair driving performance in the laboratory.

However, there are three important points to make in interpreting these data:

1) Crash data, although imperfect, often fail to indicate a substantial crash risk when patients take antihistamines and drive (6, 7). Our most serious concerns about crash

studies are: (a) crash studies usually take a very long time to perform which introduces more error in collection, analysis and interpretation; (b) often only fatal crashes are examined; (c) the base rate of drug use in most accident samples is low; (d) blood samples may be inaccurate following emergency medical care and/or death; (e) small sample sizes may preclude determination of risk for uncommon events; and (f) the person taking the impairing agent may not be examined for the presence of the offending agent;

2) Antihistamines have been classified based upon subjective drowsiness and not based on objective impairment. Clearly, it is much easier to determine that a drug causes subjective drowsiness (by looking at adverse events or by eliciting symptoms from study subjects) than it is to determine objective impairment, which requires a battery of validated tests or real world performance; and
3) Few studies have looked as whether subjective reports of drowsiness predict objective impairment. Indeed, our study showed that "subjective drowsiness either did not predict driving performance measures or was a relatively weak predictor..." of performance impairment (1). We concluded that drivers "... are probably mistaken if they believe that lack of drowsiness means that they will be able to drive without impairment."

Issues:

1. Subjective drowsiness appears to be a poor predictor of objective performance impairment (1). Objective impairment is at least as important an endpoint as subjective drowsiness. This leads to the obvious conclusion that drugs should be evaluated for their capacity to cause both subjective drowsiness and objective performance impairment.

In addition, studies should be conducted that determine whether <u>any</u> subjective symptom is useful in predicting objective performance impairment. This is important information for patients to be able to predict that they are impaired so that they can avoid situations in which a medication may be impairing or avoid an impairing medication altogether.

2. How should impairment be determined?

Should laboratory studies be designed to examine whether patients meet minimal levels of performance (criterion referenced assessment) rather than to determine the presence or absence of statistically significant differences between or among treatment groups? Are standards available on which to base guidelines so that drugs can be tested and confirmed to be impairing or not impairing?

We conclude that standards are not available and should be developed by the Agency or others. Moreover, Agency guidance should be provided to describe how drugs should be evaluated for impairment.

Manufacturers would certainly benefit from such guidance, to evaluate drugs in various classes to determine whether these agents are potentially impairing or not impairing.

Obviously, studies to test and confirm safety must be designed to show that the results are valid and can be generalized to the real world.

Recommendation:

We recommend that individual laboratory studies should not be evaluated on their own to determine whether antihistamines are impairing or not impairing. As the editorial that accompanied our manuscript suggested: "Studies that correlate these experimental measures of driving impairment and the occurrence of real-life motor vehicle crashes and determine the clinically important decrement are still needed. Also important is the conduct of studies in real-life settings that overcome the limitations faced by the nonexperimental studies."

We recommend that standards should be developed to provide a basis on which to evaluate drugs for impairment. We are not aware that standards exist. Validity evidence should be gathered to ensure that the standards generalize to real-world conditions.

Until such standards are developed, which will allow a full evaluation of drugs for impairment, no action should be taken to classify drugs as impairing or non-impairing, especially on the basis of drowsiness alone.

We conclude that the decision to classify certain antihistamines as "nonsedating" does not confer upon these drugs a classification as "nonimpairing." We cannot recommend that "nonsedating" antihistamines be switched to OTC status until guidance has been produced to define and measure "impairment" and until replicate studies with sufficient samples sizes have been performed.

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