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September 8, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1601
Rockville, MD 20852

RE: Docket No. FDA-2023-N-2653 ''Nonprescription Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments''

The Consumer Healthcare Products Association (CHPA)[1] appreciates the opportunity to comment on the upcoming Nonprescription Drugs Advisory Committee (NDAC) meeting to discuss oral phenylephrine efficacy as a nasal decongestant.[2] CHPA is supportive of the FDA goal of ensuring that consumers have access to safe and effective nonprescription medicines.

CHPA has conducted an exhaustive evaluation of all of the clinical studies on phenylephrine, both in cold and allergy populations. Additional study reports and clinical study protocols were obtained via a Freedom of Information Act (FOIA) Request. While CHPA respects the FDA's evaluation and conclusions in their Briefing Document for the NDAC on phenylephrine,[3] CHPA has differing conclusions based on the clinical data. The following outlines key information and misconceptions that CHPA would like to address for the record.

Protocol for Study BEI 1025 (Cohen 1975)

FDA notes in the Briefing Document that they were not able to access the protocol for the BEI 1025 study, the largest phenylephrine efficacy study performed in subjects with the common cold (Cohen 1975).[4] As a result of their inability to review the protocol, FDA raised a number of concerns specifically related to controlling for bias, subjective scoring and whether clinically meaningful results were obtained.

The study report for BEI 1025 containing detailed study results and the study protocol[5] was obtained by a CHPA member company via FOIA request. CHPA responses to several of the

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[1] The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of consumer healthcare products, including over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. CHPA is committed to empowering self-care by ensuring that Americans have access to products they can count on to be reliable, affordable, and convenient, while also delivering new and better ways to get and stay healthy. Visit www.chpa.org.

[2] https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-september-11-12-2023-meeting-nonprescription-drugs-advisory-committee-meeting-announcement

[3] FDA Briefing Document, Efficacy of Oral Phenylephrine as a Nasal Decongestant; Nonprescription Drug Advisory Committee Meeting, September 11 and 12, 2023; Division of Nonprescription Drugs 1 (DNPD1) Office of Nonprescription Drugs (ONPD); Division of Inflammation and Immune Pharmacology (DIIP) Office of Clinical Pharmacology (OCP); Division of Epidemiology II (DEPI-II) Office of Surveillance and Epidemiology (OSE)

[4] "… to our knowledge that protocol [BEI 1025] was not submitted to the docket and could not be reviewed as part of our retrospective review."

[5] OTC volume number 040288B; Cohen BM. Objective and subjective evaluation of phenylephrine HCl (5 mg) tablets versus placebo tablets. Study BEI 1025 volumes I-IV.

points raised by FDA about the BEI 1025 study in their Briefing Document are included below. The FOIA request clinical study materials are included as Appendices 1, 2 and 3.

FDA Briefing Document: "… there were issues with this study, including: that the methodology to reduce bias and the scoring methodology were not specified, and no adjustments were made for multiplicity."

CHPA response: The study protocol, in addition to randomized allocation of patients to the treatments, describes techniques for bias control in the Methods section.[6] In particular, point 4 describes a key aspect undertaken to reduce bias – "*Neither the investigator or the patient or other personal having contact with the patients will know the identity of the contents of the envelopes*." The scoring methodology is described in the protocol. Multiplicity, though not performed, wouldn't matter when p-values are so significant for all timepoints past 15 min (p-value$\leq$ 0.001).

FDA Briefing Document: "Since we were unable to review the protocol, it is not clear how symptoms were rated…. we do not know the frequency of the scoring, whether it was instantaneous or reflective, and how much weight was placed on subjective investigator judgement, which we know is often biased and is no longer accepted by the Agency as part of drug registration trials."

CHPA response: The protocol clearly describes the rating scale[7] and how frequently subjects were asked to record the effect of treatment on their initial cold symptoms.[8] Description in the FDA Briefing Document of both subjects and investigators scoring subjective is misleading.[9] Subjects rated their subjective symptoms at individual timepoints; the investigator did provide an initial and final symptom assessment but did not assess individual timepoints as noted in the Briefing Document.

FDA Briefing Document: "… the study did not specify what difference in absolute change might be clinically meaningful. Therefore, overall, the clinical value of this study is questionable."

CHPA response: Study investigators did provide a description of clinically meaningful in the study report - "…*patients are most likely to notice desirable medical or biological changes in their own condition when the tests improve by a minimum of 20%*".[10] Several references were

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[6] Points 3-5 of the Methods described in the 'Protocol for a subjective placebo controlled study involving phenylephrine tablets (5 mg)'. See page 92 of Appendix 1.

[7] At baseline subjects scored symptoms to the following scale - 0=none; 1=mild; 2=moderate; 3=severe; 4 very severe. After treatment, subjects were asked to write down the number which most accurately described the effect that treatment had on their cold symptoms according to the following scale – 4 = not present; 3 = much better; 2 = moderately better; 1 = slightly better; 0 = no change; -1 = slightly worse; -2 = moderately worse; -3 = much worse; -4 = very severe. See page 81 of Appendix 1.

[8] 0 min, 15 min, 30 min, 1 hour, 2 hours, 4 hours, 4.5 hours, 5.5 hours, 8 hours, 8.5 hours, 12 hours, 12.5 hours. See page 82 of Appendix 1.

[9] "Baseline symptoms appear to have been rated on a scale of 5 from mild to very severe, with improvement rated on a 0-2 scale with 0 being no change and 2 being much improved, and this evaluation appears to have been performed by both the subjects and investigators." See FDA briefing Document page 59.

[10] See page 11 of Appendix 1.

cited in support of this statement. In the Cohen 1975 study, the reduction in nasal airway resistance (NAR) at 30, 60 and 120 minutes were within this range. Assessment of 'clinically meaningful' effects using a variety of metrics (anchor-based or distribution-based) was recently computed based on the Cohen 1975 subjective data. We observed clear evidence that not only are all timepoints past 15 minutes highly significant, but also clinically meaningful.

FDA Criticism of Elizabeth Biochemical Laboratories Studies

In several instances throughout the Briefing Document, the Agency calls into question the legitimacy of the data underlying the Generally Recognized As Safe and Effective (GRAS/E) status of phenylephrine. As an example, FDA notes that Elizabeth Biochemical Labs "*…produced near textbook perfect results that could not be duplicated in other similarly designed studies that used the same methodology but were conducted at two other centers by the same sponsor. This raises suspicion regarding potential bias and data integrity issues…*"[11]

When discussing the Huntingdon #1 study, which failed to observe a difference between PE 10 mg and placebo, FDA references Table II from the Huntingdon #1 study report on standard deviation (SD) values, created to address the question of why the Huntingdon investigators could not duplicate the positive efficacy results. FDA says that lower SD values at the Elizabeth Labs study site (compared to Huntingdon) can only be interpreted in 1 of 2 ways – "*excellent study management that could not be duplicated ….. or they reflect data that are simply too good to be real.*"[12]

FDA did not mention other factors that could have contributed to the lack of observed efficacy noted by the study investigators in the Huntingdon #1 study report, including that several technicians were operating the instrument used to measure the primary endpoint (NAR) and that it was likely that few (if any) were able to optimally measure NAR. Also, the study report noted that the maximum effect of 50 mg phenylpropanolamine (PPA) was smaller in the Huntingdon study (20% decrease) compared to those observed in other studies (45% and 48% decreases observed in Cintest and Elizabeth Biochemical Labs studies, respectively).

CONCLUSION:

When considered in its entirety the evidence base for the efficacy of phenylephrine as a nasal decongestant is strong. The GRAS/E status of phenylephrine is supported by multiple double-blind, placebo-controlled trials demonstrating efficacy, confirmed by two previous FDA advisory panels, and validated by a meta-analysis of relevant clinical studies. Further, decades of real-world usage highlighting the significant role phenylephrine plays in public health has corroborated both its safety and efficacy.

In a 2006 response letter to Congressman Henry Waxman supporting the GRAS/E status of phenylephrine,[13] FDA noted that "[t]*he conclusion about the effect of an active ingredient in light of both positive and negative trials is made based on the totality of findings and quality of the data*." In light of this, it is not appropriate to speculate that data integrity issues are the

[11] See Section 3.1 'Summary of Findings'
[12] Section 3.3.3.6 'Potential Data Integrity and Other Issues in the Sterling-Winthrop Studies'
[13] FDA letter to Congressman Henry Waxman (September 13, 2006) responding to Waxman letter sent August 23, 2006.

underlying reason for failure to replicate efficacy results without any substantiating evidence backing up the assertion.

It is also important to remember that although science continually evolves, historical data or data generated through use of technology once considered state of the art but no longer used, are not invalidated simply because more modern methods or more recent data are available. New information must be assessed both in the context of its relevance to the previously generated data as well as in light of any inherent methodological limitations.

We believe new clinical data since the 2007 Advisory Committee Meeting is not conclusive evidence to support a change to the GRAS/E status of phenylephrine, as the majority of these studies had significant methodological issues and one was terminated early due to an inability to recruit the planned sample size (neither of which FDA would permit for new drug approvals).

Thank you for the opportunity to submit this information. We look forward to the NDAC meeting on September 11.

Regards,

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