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THE PROPRIETARY ASSOCIATION

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May 15, 1985

Dockets Management Branch [HFA-305]
Food and Drug Administration
Room 4-62
5600 Fishers Lane
Rockville, Maryland 20857

RE: [Docket No. 76N-052N; Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drug Products for Over-the-Counter Human Use: Tentative Final Monograph for OTC Nasal Decongestant Drug Products]

Dear Madam:

The January 15, 1985 Federal Register contained the above notice of proposed rulemaking. Interested persons were invited to submit written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs by May 15, 1985.

These comments are filed on behalf of The Proprietary Association, a 104-year-old trade association, the active members of which are engaged in the manufacture and distribution of nonprescription, over-the-counter medicinal products. Members of the Association are subject to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301, et seq.) and are interested in and affected by this proposal.

These comments are not intended to supersede any others that may be filed by individual members of the Association.

GENERAL COMMENTS

1. Legal Status of Monographs

The Association notes its continuing position that Monographs issued under the OTC Review are interpretive, as opposed to substantive, regulations. The Association's views on this subject were presented in its March 4, 1972 comments on the Proposed Procedures for Classification of Over-the-Counter Drugs, and its June 4, 1973 comments on the Proposed Antacid Monograph.

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2. Exclusivity Policy

The Association also notes its continuing position that FDA cannot legally and should not, as a matter of policy, prescribe exclusive lists of terms from which indications for use for OTCs must be drawn and prohibit alternative OTC labeling terminology to describe such indications which is truthful, not misleading and intelligible to the consumer.

The Association's views on this subject were presented in oral and written testimony submitted to FDA in connection with the September 29, 1982 FDA hearing on the exclusivity policy.

We note that a proposed revision to this policy was published on April 22, 1985 and the Association will be submitting further comments on that proposal.

3. The Terms "Caution" and "Warnings" in Labeling

The Proprietary Association objects to the proposed elimination of the term "caution(s)" on the labeling of OTC products. To the lay consumer, there is a distinct difference between the term "warning(s)" and the term "caution(s)." The analogy is perhaps to red flashing lights at a railroad crossing, a clear warning signal not to cross; and the flashing yellow highway caution signal advising motorists to slow down and to proceed carefully through an intersection.

The word "warning" is significantly harsher than "caution." A warning governs how a product is to be used and even precludes use under certain conditions. In addition, a warning often refers to immediacy of the danger of misuse.

A caution, on the other hand, does not preclude use unless something occurs during use but often alerts the consumer to a potential problem. It may also address a monitoring function to be performed while the product is in use.

While both types of statements are usually used to call attention to potential danger, the distinction between them is important, particularly when products contain long lists of warnings. It is important for the consumer to be able to distinguish at a glance between precautionary statements and more serious warnings. Since the same phrases may be warnings with regard to one class of products and merely cautions with regard to another, the flexibility to use both terms is essential in order to prepare accurate and comprehensible labeling.

SPECIFIC COMMENTS

1. Phenylpropanolamine Preparations

The Proprietary Association regrets that phenylpropanolamine preparations have been omitted from the Tentative Final Monograph (notice of proposed

rulemaking). As noted at (50 Fed. Reg. 2221), 3rd column, the omission is based on the agency's ongoing review of comments submitted in both the OTC weight control and nasal decongestant rulemakings. These comments were submitted in response to FDA's request for information relating to the extent, if any, that phenylpropanolamine induces or aggravates hypertension.

Unfortunately, the omission might be seen as suggesting that the agency has reason not to concur with its own advisory panel which reviewed the then more than 40 years (now 50 years) of safe use of OTC nasal decongestant preparations with phenylpropanolamine in the U.S. However, the evidence on which the agency's concerns are apparently based have not been provided.

The Association believes that the experience with phenylpropanolamine as a nasal decongestant at the currently marketed immediate release dose levels have not resulted in adverse reactions of such quality or quantity to suggest that the drug is unsafe for use at these doses in cold/cough preparations. The Association believes that the agency should proceed within the scope of the OTC Review to resolve as promptly as possible any outstanding questions it may have regarding the safety of phenylpropanolamine as a nasal decongestant. As the agency is aware, a number of companies have advised that they will be submitting additional data before the close of the administrative record for this docket.

2. Indications for Use (Section 341.80(b))

The Proprietary Association notes that some distributors of products containing nasal decongestants have limited their intended target populations to persons suffering from colds or cold-like symptoms. Others have restricted their appeal and promotion to persons with allergic rhinitis (hay fever) and other upper respiratory allergies. Such strategies are called "positioning" or "segmenting a market".

"Positioning" of a product to appeal to a particular segment of the consumer market is a long established marketing principle. Put simply, the term in the modern sense is used to mean the strategy by which a product's label, buttressed by advertising and promotion, communicates to the target population (market segment). A product whose message is unclear or "blurred" seldom succeeds in the marketplace. Consequently, clear, concise and accurate labeling statements are essential elements in a product distributor's efforts to convey his message to a specific target population and thus serve to establish his product's position in the marketplace.

It is well recognized that many cold/cough products are combinations of ingredients from different pharmacologic categories. Two, three, and even four-ingredient combinations are not uncommon. The CCABA Panel identified fourteen combinations of ingredients from up to three different pharmacologic groups which the Panel believed were generally recognized

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as safe and effective. In a feedback communication to an industry member, FDA has identified another safe and effective combination, a four-ingredient combination composed of a Category I analgesic, anti-histamine, antitussive, and nasal decongestant.

Industry marketing studies show that many consumers with a cold prefer to purchase small packages of a product to treat a single cold or to combat the particular symptoms which they may be experiencing at the moment. Small packages of multi-ingredient combination products contain little label space for necessary indications and warnings. It is therefore important for the distributor of a product to have the option to eliminate indications which are not applicable to a particular segment of the market for which his product is positioned.

Further, if a product is clearly identified as a cold medication through its trade name, advertising, marketing strategy, and shelf-positioning, the Association submits that indications for hay fever or allergic rhinitis just because the product may contain an antihistamine (which has other uses in connection with the common cold) would appear to be extraneous.

The Association requests, therefore, that Section 341.80(b) be amended to provide distributors of Category I OTC nasal decongestant drug products and appropriate Category I OTC combinations of nasal decongestants and other ingredients with the option of including label indications pertaining to relief of nasal congestion due to any one of the following:

- a. colds or the "common cold";
- b. hay fever (allergic rhinitis) or other upper respiratory allergies;
or
- c. both colds and hay fever.

3. Other Allowable Indications (Section 341.80(b)(2))

The Association assumes that the "other allowable indications" listed in the above referenced section of the TFM may be identified on product labels as "other indications" if they are separate from the indications identified in Section 341.80(b) and are not given greater prominence. The Association believes that the following underlined terms are closely similar — perhaps even synonymous — to claims in the "other allowable indications" section; further they are meaningful to the consumer and may also be used in labeling, e.g., "temporarily relieves" or "for the temporary relief" of "stuffed-up head, stuffy head" in addition to "clogged-up nose" and "stuffy nose."

4. Warnings for OTC Topical Nasal Decongestant Drug Products (Section 341.80(c))

- a. The warning "do not exceed recommended dosage because burning, stinging, sneezing or increases in nasal discharge may occur" (50 Fed.

Reg. 2239, first column) does not appear to be justified on the basis of consumer information and should be deleted from the Monograph.

One major PA member firm reviewed its consumer complaint file on nasal sprays over a period of five years and found that the average complaint rate was less than one complaint per million packages sold. This strongly suggests that consumers do not experience a problem with "burning/stinging" following use of decongestant nasal sprays. Other PA members report similar data. Further, the warning states that the reactions of "burning, stinging, sneezing, or increase of nasal discharge" will be the result of exceeding the recommended dosage. The logic of this cause and effect is questioned as it applies to nasal sprays and drops. Even if an excessive amount of spray or drops is used, and this seems highly unlikely, the solution will either run out of the nose or drain to the back of the throat or both. In either case the amount of liquid that will adhere to the nasal mucosa is relatively constant.

- b. The proposed new warning statement for topical nasal decongestants except inhalants: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland unless directed by a physician" is not appropriate and should be deleted from the Monograph (Section 341.80(c)(2)(iii)(b))

FDA seems to be concerned that systemic effects can occur as a result of absorption from the gastrointestinal tract if an excessive amount of topically applied nasal decongestant drug is swallowed. The PA is unaware of any data that support the agency position that an excessive amount of drug can be, or is, swallowed when the product is used as directed. The Association submits that this may be conjecture on the part of the agency.

It is well established that the dose delivered from a nasal spray (squeeze bottle) is not precise. The amount depends on how the consumer squeezes the bottle and whether he/she applies two or three sprays in each nostril per label directions. The range of the amount delivered is usually 200-400 mg. of total product on a weight basis per dose. If one assumes that the average amount delivered per dose is 300 mg. of product and assumes that all (100%) of this amount is swallowed (which is not possible), one could then calculate the amount of drug swallowed. In the case of phenylephrine hydrochloride the major commercial use is a 1/2% nasal spray which delivers per dose an amount of active ingredient equivalent to 1.5 mg. Using the above information the maximum amount of phenylephrine which might be swallowed would only be 1.5 mg. which is only a small fraction of the Category I recommended oral dose of 10 mg.

A similar argument can be made for nose drops containing 0.5% ephedrine sulfate where the average typical adult dose is approximately 0.6 mg. Again, if 100% of the dose was swallowed (which is

not possible) the subject would swallow only 0.6 mg. of ephedrine sulfate. Noting that the CCABA Panel (41 Fed. Reg. 38408, September 9, 1976) concluded that ephedrine and any of its salts is safe in the oral dose range of 8-12 mg., it is apparent that only a very small fraction of the usual oral dose could be swallowed (approximately 6%). Since there is no recognized oral dose for oxymetazoline or xylometazoline, similar calculations cannot be made for these two compounds.

The Association requests that the proposed warning statement in its entirety be deleted from the Final Monograph. As additional support for this position, the Association is attaching as Appendix A a summary of published studies which address the issue of intranasally applied decongestants and possible cardiovascular changes.

c. Proposed Warning for 1% Phenylephrine Hydrochloride

The Association notes that support for this proposal is referenced on page 2229 of the Tentative Final Monograph i.e., Comment No. C0125 (one study by BCRI and one by Jolly, et al.) and a letter from Dr. W. Gilbertson to Sterling Drug Inc.

The Association has reviewed the studies submitted under Comment No. C0125 and believes the data are insufficient to warrant the proposed warning for the following reasons.

The agency itself admits that ". . . the difference in side effects between the two groups (0.5 percent vs. 1 percent phenylephrine) were not statistically significant" (50 Fed. Reg., 2229). FDA also states that the 1 percent concentration of phenylephrine "seemed more likely" (i.e., suggestive) to induce rebound congestion and that this effect was at best only "possible" (50 Fed. Reg., 2229). The Jolly, et al., paper confirms this view as follows:

"The higher incidence of responses which probably reflects rebound hyperemia in the 1 percent group (19 percent) as compared to the 0.5 percent group (4 percent) is of questionable significance from the statistical standpoint" (page 281 of Comment C0125).

An in-depth review of the cited studies shows that even the suggestive evidence in this case is insufficient to support a possible link between rebound congestion and the frequent use of 1 percent phenylephrine. For example, the study by Jolly, et al., itself questions the reliability of the method used for assessing side effects:

"It must be emphasized that even under optimal conditions rating erythema and edema of mucosal

surfaces is a highly subjective procedure and that decisions frequently and properly are forced. Supporting this thesis is that the mean subjective nasal patency scores, generally a more reliable index of the actual state of the nasal mucosae, decreased slightly. Mean scores for direct observation for the 0.5 percent and 1.0 percent solutions remained comparable throughout the study period." (Page 281 of Comment C0125).

The Association points out that, even if one were to assume the method of data collection on side effects used by Jolly, et al., was unquestionable, the two studies are not confirmatory in relation to the "possible" effect seen in the Jolly, et al., study.

Finally, neither study provides definitive data concerning the use of prestudy medications containing nasal decongestants or concerning the baseline conditions (allergy or colds) of those individuals who were reported to experience the side effect of congestion during drug usage periods. Thus, critical information is missing from the assessment of side effects in these studies relative to (a) discontinuance of prestudy drugs at study onset with resultant rebound congestion during the study and (b) the effect of baseline conditions on the occurrence of reported side effects (i.e., drug/disease interaction).

In summary, the studies submitted in support of the efficacy of 0.5 percent and 1 percent phenylephrine were designed to assess efficacy. The methodology was not sufficiently sensitive to define confidently a comparative safety profile for the two concentrations of phenylephrine. The investigators questioned their methods, did not find statistically significant effects, and failed to report certain key information in defining drug-induced side effects. Thus, the Association believes that suggestive data forming at best a possible link of a side effect are insufficient to warrant a label warning for products containing 1 percent phenylephrine and requests that the proposed warning be deleted from the Final Monograph.

5. Proposed Warning For Oral Nasal Decongestants Containing Phenylephrine Hydrochloride, Pseudoephedrine Hydrochloride, or Pseudoephedrine Sulfate When Labeled For Adults And For Children Under 12 Years of Age, e.g., Proposed Subsections 341.80(c)(1)(i)(b) and 341.80(c)(1)(ii)(b). "Do not take this product for more than 7 days. If symptoms do not improve or are accompanied by fever, consult a doctor."

As written, these proposed warnings appear to advise against the use of Category I OTC oral decongestants without first consulting a doctor if a fever is present initially. The Association wishes to point out that the

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agency's ANPR for OTC internal analgesic/antipyretic drug products (42 Fed. Reg. 35346-494, July 8, 1977) classified as Category I, combinations of one or two Category I internal analgesic/antipyretic ingredients "with generally recognized as safe and effective nasal decongestant active ingredient(s) provided the product is labeled for the concurrent symptoms involved . . ." including "for the reduction of fever." (42 Fed. Reg. 35370, second and third columns).

Oral nasal decongestants have been used over the counter for many years and billions of doses have been sold without such a label warning. We are unaware of any safety problems that have occurred as a direct consequence of a consumer using a nasal decongestant in the presence of minor fever of short duration, which is the case in the vast majority of instances in which fever is present.

On the other hand, the presence of high fever is of importance to the well-being of the consumer and a doctor should be consulted in such instances.

The Proprietary Association requests that the above-referenced warnings should be amended to read:

"(b) If symptoms do not improve in 7 days or are accompanied by high fever, consult a doctor."

Some allergic episodes (and even colds) occasionally continue for more than 7 days, particularly in humid climates or in periods of high pollen counts. Thus an absolute 7-day use limitation may not always be appropriate.

The Association also submits that its amended warning would be equally informative to consumers who may be taking an oral nasal decongestant product without an antipyretic ingredient as well as to those who may take a combination which includes antipyretic ingredient(s). PA requests that its amended warning be included in the Final Monograph for (1) OTC nasal decongestant drug products; (2) OTC internal analgesic/antipyretics; and (3) OTC cold/cough combination products.

6. Recommendations for Changes in Pediatric Dosage Schedules

The Association is aware of recommendations for changes in pediatric dosage schedules for a number of medications that have been advanced by McNeil Laboratories and believes that the Agency should give serious consideration to such proposals. The Association is also aware that McNeil and other companies plan to submit additional data in the near future on this subject.

The Association's recommendations may be summarized as follows:

- a. an optional dosage schedule for oral drugs which utilizes the concept of a pediatric dosage unit equivalent to 1/8 the adult dose and includes additional age groupings developed to better utilize the pediatric dosing unit concept; and
- b. a standardized weight base schedule that could be incorporated on an optional basis as part of the dosing recommendations in consumer package labeling.

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Recommendation "a": New Pediatric Dosing Schedule Based on a Pediatric Dosing Unit (PDU).

Most cough-cold products currently available in the nonprescription market place are targeted toward either adult or pediatric patients. For those products targeted toward adults, which also incorporate some dosage recommendations for the pediatric patient, it is reasonable to continue to allow the dosing schedule currently in the Tentative Final Monograph. However, for products primarily intended for pediatric use, there is a need for a dosing schedule that would provide for greater ease of administration of smaller dosage units to the pediatric patient. With regard to the latter, adoption of a dosing system based on a pediatric dosing unit, as currently used in the analgesic/antipyretic Proposed Monograph, would provide a consistency between various monographs and allow for consistency in the formulation of combination products.

Pediatric Dosing Unit (PDU) System

The concept of a pediatric dosing unit is a concept developed to provide for a dosing unit that will allow dosing of pediatric formulations in a manner consistent with the need of the growing pediatric patient, with incremental dosing throughout the entire pediatric (under 12 years) age range and with incremental age and weight ranges that are consistent with the typical growth pattern in children. Based on careful review, it was determined that the most appropriate PDU, consistent with the above criteria, would be a pediatric dosing unit that is one-eighth of the adult dose. Other fractions of the adult dose, such as one-twelfth, one-tenth, one-fifth, do not meet the needs for pediatric formulations as satisfactorily. In addition, a pediatric dosing unit that is one-eighth of the adult dose is consistent with the pediatric dosing unit already in use with acetaminophen and aspirin products. A pediatric dosing unit determined in this fashion can be applied independent of drug half-life and dosing intervals as long as dosing intervals can be adjusted to take into account drug elimination rates. Using the PDU systems, a dosing framework can be developed which uses incremental age periods or incremental weight ranges. The incremental age periods are consistent with currently recommended dosing schedules for acetaminophen and aspirin. For products whose labeling is limited to children ages 2 and older, only six such age breaks would be incorporated into package labeling. Professional labeling could be subsequently developed for the additional age breaks.

Recommendation "b": Weight-Based Dosing Schedule

There is an additional benefit to consumers to have optionally available weight related dosing schedules for use with children when weight is known, especially when children are very large or very small for their age or when children approach the usual age breaks for a given dosing schedule. While dosing of drugs in the pediatric patient has been recommended on the basis of age, weight, and body surface area, and while each of these parameters can be interrelated, there are some specific advantages in each approach. While body surface area may reflect more accurately the magnitude of change that occurs in the growing child, body surface area is not a growth parameter that is in common use in the

pediatricians' offices and is clearly not a parameter that is used by parents. As a result, the use of weight as a parameter for dosing of drugs has far more practical merit. Weight changes are reasonably similar to the changes in body surface area and thus, dosing by weight is a reasonable substitute for dosing by body surface area. However, weight is not always known at the time of dosing recommendation by a physician or when a parent is making a decision. Age has the advantage that is almost universally known and is the simplest parameter for consumer use. As demonstrated above, age can be used as a reasonable guide to growth in the child provided one takes into consideration the wide variations in growth that occur in the pediatric population. Nonetheless, having available a weight-based dosing schedule offers a significant benefit for those consumers or health professionals who would like to dose by weight. We would recommend, however, that the weight-based schedule be an optional schedule, since weight is not always known.

In order to avoid unnecessary consumer and health professional confusion when such weight-based schedules are made available, it would be beneficial to have a standardized weight schedule for all pediatric dosing products.

The Association appreciates the opportunity to express its views in connection with the above referenced Federal Register document.

Sincerely,

THE PROPRIETARY ASSOCIATION



Alan W. Mercill
Vice President-Technical Affairs

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Enclosure: Appendix A: Summary of Published Evidence Relating to the Issue of Intranasally-Applied Decongestants and Possible Cardiovascular Changes