

BRISTOL-MYERS PRODUCTS

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

Docket No. 76N-052N
Tentative Final Monograph
for Over-The-Counter Nasal
Decongestant Drug Products

Gentlemen:

Bristol-Myers Products (BMP) a manufacturer of over-the-counter (OTC) pharmaceutical products including, specifically, nasal decongestant products wishes to offer the following comments concerning the notice of proposed rulemaking. Tentative Final Monograph for OTC Nasal Decongestant Drug Products. 50 Fed. Reg. 2220 (January 15, 1985).

- 1.) Proposed section 341.80 (c)(1)(i)(b), as written, can be read to warn against use of OTC nasal decongestants not only if fever persists but if fever is present initially. Perhaps such a warning would be of limited import for single ingredient products. However, the proposed warning would have a serious and unwarranted adverse effect on the use of combination products containing a nasal decongestant along with an analgesic/antipyretic.

BMP points out that combination products for the alleviation of the symptoms of the common cold are widely used and have been used safely for decades. The common cold is often accompanied by both fever and nasal congestion at the outset. A warning against even temporary use of a combination product under such conditions would deprive the consumer of the benefits of self medication. It could, in addition, lead consumers to needlessly consult physicians and thereby drive up the costs of health care. BMP notes that the Advisory Panel on Internal Analgesic, Antipyretic and Antirheumatic Products in its Proposed Rule stated with respect to combination products that:

One Category I analgesic-antipyretic active ingredient or a combination of two such ingredients...may be combined with generally recognized as safe and effective nasal decongestant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g. "For the reduction of fever and for the temporary relief of nasal congestion due to the common cold (cold)." 42 Fed. Reg. 35346, 35370 (July 8, 1977)(emphasis added).

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Proposed section 343.20(d)(3), id 35493, restates the Panel's view that when both fever and nasal congestion are present as concurrent symptoms, a combination of an analgesic/antipyretic and a nasal decongestant is a rational treatment. BMP therefore urges that proposed section 341.80(c)(1)(i)(b) be rewritten so as to expressly permit combination products containing analgesic/antipyretic ingredients along with a nasal decongestant even should fever be present, initially, along with nasal congestion.

BMP points out that such a determination would also be consistent with proposed section 341.40(m), 41 Fed. Reg. 38312, 38421 (September 9, 1976). In essence, the advice of two separate panels of experts should not be overturned.

- 2.) The TFM for OTC Nasal Decongestant drug products should be made consistent with that for Antihistamines. 50 Fed. Reg. 2200 (January 15, 1985). Although neither TFM addressed combination products, the tentative determination that

[A]ntihistamines did not reduce nasal obstruction and therefore did not aid in sinus drainage. [B]ut the studies indicated that antihistamines may sometimes further aggravate nasal obstruction. 50 Fed. Reg. at 2203 (References omitted).

should not cause the FDA to adopt a TFM for combinations of antihistamines and orally administered nasal decongestants contrary to the recommendation of the Advisory Panel on Cough Cold Products. Proposed section 341.40(b). 41 Fed. Reg. 38312, 38420 (September 9, 1976).

- 3.) As pointed out in BMP's December 13, 1983 comments submitted in response to the Antitussive TFM, 42 Fed. Reg. 48576 (October 19, 1983) there is need to harmonize the dosage regimens of cough-cold ingredients with the pediatric dosage schedule recommended by the Advisory Panel on Internal Analgesic, Antipyretic and Antirheumatic Products. 42 Fed. Reg. at 35368.

Failure to provide for the requested harmonization would result in removal of products intended for use in children below age 12 from the market once Final Rules are published for one or both groups of OTC drug products. The agency should not ignore the reality that nasal congestion along with fever and/or pain frequently occur concurrently in children as well as in adults. In such instances of concurrent symptomatology, it cannot be denied that administration of few rather than many dosage units to children can logically be expected to meet with less resistance thereby increasing compliance and benefit.

BMP therefore urges that the dosage regimen for nasal decongestants intended for oral administration to children under twelve (12) years of age in proposed sections 341.80 (d)(1)(i) and (ii) be changed to provide for five (5) separate dosage regimens. The requested change would comport with the children's dosage regimen for analgesic/antipyretic products. Failure to harmonize the various monograph proposals would yield, for example, consequences such as those illustrated below:

Children 2 to under 4 years of age - Suggested Pediatric Schedule C for acetaminophen would limit the single dose to 160 mg. of drug (2 x 80 mg. dosage units). A dosage unit containing 80 mg. acetaminophen plus 1.25 mg. phenylephrine hydrochloride would meet the proposed dosages in both the Internal Analgesic (IA) Monograph and the Nasal Decongestant TFM, i.e. 160 mg. analgesic/antipyretic and 2.5 mg. phenylephrine hydrochloride. However, the IA Pediatric Dosage Schedule C limits the dosage frequency to 5 x 160 mg. per 24 hours. Thus, the illustrative combination would permit administration of but 5 x 2.5 mg. or 12.5 mg. of the nasal decongestant in a 24 hour period. The result would be a "deprivation" of 2.5 mg. of phenylephrine per 24 hours for the pediatric consumer.

Children 4 to under 6 years of age - The IA suggested Pediatric Schedule C would limit the single dose to 240 mg. (3 x 80 mg. dosage units). The dosage unit described in the preceding paragraph would satisfy the suggested analgesic/antipyretic dose but administration of three (3) dosage units would require administration of 3 x 1.25 mg. or 3.75 mg. phenylephrine hydrochloride, an amount in excess of the single dose limitation, 2.5 mg., of proposed section 341.80 (d)(1)(i) of the TFM.

Furthermore, administration of five (5) doses of the illustrative formulation (the maximum amount permitted in suggested Pediatric Schedule C) would result in a total daily dose of 5 x 3.75 mg. or 18.75 mg. of phenylephrine hydrochloride. This would exceed the maximum 15 mg. per 24 hours given in proposed section 341.80 (d)(1)(i).

Similar arithmetic for children aged 6 to under 9, 9 to under 11, and 11 to under 12 years of age would merely emphasize the need for inter-monograph consistency. The alternative would be a plethora of dosage forms or label directions which would only confuse the consumer needlessly. BMP urges the agency to retain consistency in pediatric dosage units because:

The[IA] Panel conclude[d] that the pediatric dosage unit of 80 mg. (1.23 gr.) of aspirin [or acetaminophen] should be retained because there is long

standing acceptance. [I]t believes that basing pediatric dosage recommendations on age will be more readily understood by the average consumer.... 42 Fed. Reg. at 35368.

An equally striking incompatibility would exist for combinations of acetaminophen and pseudoephedrine salts in the consumer-convenient dosage form recommended by the IA Panel.

For children aged 2 to under 4, a dosage unit containing 80 mg. analgesic/antipyretic plus 7.5 mg. decongestant would meet the single dose recommendations of the IA Panel and proposed section 341.80 (d)(1)(ii). However, administration of five (5) doses would result in a total dose of pseudoephedrine salt of 75 mg., an amount in excess of the proposed 60 mg. per 24 hour limitation. For children 4 to 6 years of age, administration of this same dosage unit in accordance with the regimen proposed by the IA Panel would yield a 22.5 mg. of pseudoephedrine salt per single dose and 112.5 mg. in a 24 hour period. Both amounts are in excess of the dosage maxima in proposed section 341.80(d)(1)(ii).

For children aged 4 to under 6, the 24 hour maximum proposed dose would be met by a dosage unit containing 80 mg. acetaminophen plus 4 mg. pseudoephedrine salt. However, the single dose of nasal decongestant would then be 12 mg. rather than the proposed 15 mg., a twenty-five percent "shortfall." This same hypothetical dosage unit would, for children 2 to under 4 years of age, provide but 8 mg. of nasal decongestant per single dose and 40 mg. in 24 hours. Although these doses are less than those proposed in the TFM, BMP believes that such lower doses can be justified by employing the same age/body surface area extrapolations employed by the IA Panel in arriving at Pediatric Schedule C for analgesics/antipyretics.

A suggested dosage schedule for pseudoephedrine hydrochloride or sulfate to be administered to children either alone or in combination with an analgesic/antipyretic is provided below:

<u>Age of Child</u> <u>Years</u>	<u>Mg. Per Dose</u> <u>(1)</u>
2 to under 4	8
4 to under 6	12
6 to under 9	16
9 to under 11	20
11 to under 12	24

(1) Not to exceed 5 doses in a 24 hour period.

A similar schedule is easily arrived at for phenylephrine hydrochloride.

Consistent with its comments in Number 1, supra, BMP urges that the warning in proposed Section 341.80 (c)(1)(ii)(b) be reworded to explicitly permit use of orally administered Category I nasal decongestants along with antipyretic agents when there are present concurrent symptoms of fever and nasal congestion.

BMP urges that the FDA clarify the portions of the TFM commented on above as requested by the comments submitted. BMP further requests that the comments appropriate to combination products be adopted by the FDA when TFM's for combination products are published.

Respectfully submitted,



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