

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

DATE: DEC 19 1994
FROM: Director, Center for Drug Evaluation and Research
SUBJECT: CDER OTC Analgesic Policy Change
TO: Commissioner, Food and Drug Administration

Since our previous meetings with you regarding Aleve in late 1993, the Center has held extensive internal and expert advisory review of our current NDA and monograph OTC analgesic regulatory requirements and labeling indications. On September 8-9, 1994, a public joint Nonprescription Drug and Arthritis Advisory Committee meeting provided support for a consistent new regulatory approach which the Center has adopted.

CDER POLICY ON OTC ANALGESIC DRUGS

Comparable regulatory requirements and scientific standards are needed for all OTC analgesic/antipyretics whether submitted for NDA or monograph review. Under a uniform policy which will apply to all current and future products, all OTC analgesic drug products will be equitably studied, reviewed, and labeled.

Labeling indications and data requirements for this policy are presented below:

<u>Indication</u>	<u>Proof required</u>
"For the temporary relief of occasional aches and pains,"	Two positive clinical trials in appropriate pain models
"Headache,"	Positive clinical trial in an OTC headache model
"Menstrual cramps,"	Positive clinical trial in an OTC dysmenorrhea model
"Fever_"	Positive clinical trials in a fever model for both adults and children

First, analgesics must demonstrate efficacy in at least two adequate and well-controlled studies using appropriate pain models (for example, dental, sore throat, muscle strains) to receive a general indication for pain, "For the temporary relief

of occasional aches and pains." This wording simplifies the indications section of the OTC analgesic label, concurs with the original Panel proposed label for monographed analgesics, and is consistent with prescription analgesic development guidelines.

Second, if sponsors demonstrate efficacy in a single, well controlled clinical study using each pain model, headache and/or menstrual cramps may be added to the labeled pain indication. Practical and scientific reasons support separate studies and labeling for these two conditions. Further, based on proven clinical efficacy, addition of these pain indications will allow rational limited expansion of the label to accommodate consumer and sponsor preferences.

Third, in order to obtain OTC labeling for antipyresis, effectiveness must be shown in both children and adults. Children are frequently treated for fever with OTC products despite restrictive adult labeling. Thus, the agency can assess the safety and efficacy of OTC products which are likely to be used in a significant OTC subgroup for the labeled indication.

Over the past year, analgesic new drug sponsors were informed of potential policy changes and study requirements to support labeled indications. Thus, most investigational drugs under review comply with our new policy. For those products currently filed under new drug applications (for example, naproxen sodium and ibuprofen) Phase 4 demonstration of efficacy is required.

For those analgesic/antipyretic ingredients under the monograph review, nonprescription manufacturers must submit (or reference) efficacy data on aspirin, acetaminophen, and the group of nonaspirin salicylate salts. After review, labels will be approved for aches and pains, headache, menstrual cramps, and/or fever.

Therefore, all analgesic/antipyretic drug-products will be labeled "For the temporary relief of occasional aches and pains. If adequately studied in appropriate OTC pain models, some products will also be allowed the additional indications of "menstrual cramps" and/or "headache" and/or "fever.."

We appreciate your continued interest in these over-the-counter drug products. Additional written material is available for your review if you need further clarification on the background or basis for this policy change. At your discretion, we would be more than happy to meet with you to further discuss this policy change.



Janet Woodcock, M.D.

OTC ANALGESICS: LABELING CLAIMS// DATA REQUIREMENTS

Internal Analgesic Panel Recommendation

“relief of occasional minor pain, headache, and fever”

Evaluation published literature

TENTATIVE FINAL MONOGRAPH

"For the temporary relief of minor aches and pains"

which may be followed by one or more of the following:

"associated with" (select one or more of the following: "headache", "toothache", "muscular aches", "backache", "the premenstrual and menstrual periods" [which may be followed by: "dysmenorrhea"], or "premenstrual and menstrual cramps" [which may be followed by: "dysmenorrhea"], "and for the minor pain of arthritis", *and* "and to reduce fever."

OTC ANALGESIC NEW DRUG APPLICATIONS

Ibuprofen, Naproxen sodium., and Ketoprofen

-Evaluation following FDA guidelines. Once effectiveness demonstrated, allowed expanded indication.

NDAC & ARTHRITIS COMMITTEES

Considered naproxen sodium. During deliberations, questions raised regarding adequacy of data to support labeling/expanded indication.

NDAC & ARTHRITIS COMMITTEES

Committees met with experts to address data requirements/recommendation.

Indication (temporary relief of)	Data Required for Effectiveness
minor aches and pains	two positive clinical trials in appropriate pain models
headache	one positive clinical trial in an OTC headache model
menstrual cramps	one positive clinical trial in an OTC dysmenorrhea model
fever	one positive clinical trial in a fever model for adults and one separate positive trial in children

CLASSIFICATION OF MONOGRAPH INGREDIENTS BASED UPON RECENT STANDARDS

Ingredient	Aches pains	Headache	Fever	Menstrual cramps
Acetaminophen	I	I	2	III
Aspirin	I	I	Z	I
Carbaspirin calcium	I	I	T	III
Choline salicylate	Z	z	I	III
Magnesium salicylate	I	I	I	ZII
Sodium salicylate	I	I	I	III

DECEMBER 1994 MEMORANDUM RE: CDER POLICY

- Comparable regulatory and scientific standards for all ingredients
- Limited claim [no other claims would be allowed]
- **For the temporary relief • minor aches and pains
• headache • menstrual cramps and fever**

MEMORANDUM IMPACT:

TERMS DISALLOWED THAT WERE INCLUDED IN TENTATIVE FINAL MONOGRAPH MINOR
ACHES AND PAIN ASSOCIATED WITH

- A COLD
- THE COMMON COLD
- SORE THROAT
- TOOTHACHE
- MUSCULAR ACHES
- BACKACHE
- THE PREMENSTRUAL AND MENSTRUAL PERIODS
- DYSMENORRHEA
- MINOR PAIN OF ARTHRITIS

