

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

MEMORANDUM

DATE: April 5, 2001
FROM: OTC Antihistamine Review Team
TO: Pulmonary and OTC Advisory Committee Members, Consultants and Guests
THROUGH: Division of OTC Drug Products
SUBJECT: May 11, 2001 Advisory Committee Meeting to Discuss OTC Antihistamines

Background

The following information is included in your background package:

- the initial panel report addressing the issues of OTC antihistamines;
- the tentative final monograph describing the initial labeling and acceptable ingredients for OTC antihistamine use; and
- the final monograph.

These documents describe the regulatory process of ingredients which have been categorized as Generally Recognized as Safe and Effective (GRAS and GRAE). This information provides the labeling and categorization of ingredients, which are acceptable for marketing under the cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use monograph.

The remainder of the discussion that follows concerns the new drug side of OTC drug development. The principles of that help to define the OTC availability of drugs products date back to 1951 with the passage of the Durham-Humphrey Amendment, which identified three conditions or categories of drugs that would be limited to prescription (Rx) use:

- certain habit-forming drugs listed by name in the Food Drug & Cosmetic Act;
- drugs not safe for use except under supervision of a licensed practitioner; and
- drugs limited to prescription use under an NDA.

In 1998, this was amended to eliminate certain habit-forming drugs as a specific condition. Thus, the Agency has interpreted the Durham-Humphrey Amendment to mean that any drug that can be used safely over the counter should be.

OTC Switch Process

FDA's OTC MaPP (6020.5) outlines the regulatory responsibilities and processes for switching of products from prescription-only to OTC status and for direct OTC drug development for a new drug (which has not previously been marketed as a prescription product). The question that is often asked and will be addressed today is when is it appropriate for a product to move from a prescription into an OTC realm. To address this issue it is important to consider some of the details of the OTC switch process.

OTC switches can be of several types. First, there is the complete switch in which all of the doses and all of the indications, which are currently marketed, Rx is taken over the counter. This eliminates the need for a prescription product. The second type is a partial switch in which some

of the doses and some of the indications are taken over the counter, and some remain unchanged in the prescription form. The third option, which is not really a switch, is the marketing of a lower dose of a prescription product and/or the marketing of the product with a new indication that would not require a learned intermediary's intervention.

The following issues were identified as "Switch Principles" in the early 1990s (expounded by Carl Peck, M.D.) and remain useful in deciding which drugs may be suitable candidates for OTC switch.

1. Does the switch candidate have special toxicity in its class?
2. Does the candidate have a large margin of safety?
3. Does the candidate's frequency of dosing affect its safe use?
4. Has the candidate's safety profile been defined at high dose?
5. Has the candidate been used for a sufficiently long time on the Rx market to enable a full characterization of its safety profile?
6. What is the worldwide marketing experience of the switch candidate?
7. What foreign countries market the candidate OTC? What is its experience in those countries?
8. What do the "use data" (from National Prescription Audit, the National Drug/Disease Audit and/or other sources) show?
9. Has a vigorous risk analysis been performed?
10. Has the efficacy literature been reviewed in a way to support the expected usage and labeling of the switch candidate?
11. Is there a full understanding of the pharmacy-dynamics of the switch candidate?
12. Is the minimally effective dose for the proposed OTC indication known?
13. Have possible drug interactions for the switch candidate been characterized?

Clearly doses that are felt to be acceptable must be relatively safe, with a reasonably acceptable safety margin, and the product must have a low misuse or abuse potential at the recommended labeled dose(s). Further, consumers should be able to understand when to use the product, what are the potential benefits and risk, and how to use the product.

Data to support the OTC switch generally comes from the following sources: efficacy trials, safety data, actual use trials, and label comprehension trials. Efficacy data may not need to be presented if efficacy was already established for the proposed dose and dosing regimen during clinical development of the prescription product. However, for lower doses or new indications efficacy information is essential. Safety assessments typically rely on information presented in the NDA, worldwide databases, FDA's Adverse Event Reports (AERs) database (post-marketing) and literature. Actual use trials are trials designed to assess how consumers actually use the product in an OTC-like setting. These trials are usually open label and are designed specifically to assess consumer use, but they may also provide information about safety. Label comprehension trials are designed to assess understanding of the labels. These latter two trials may or may not be needed depending upon the product, and whether there are any unique issues related to use, warnings or directions that would need to be tested prior to marketing.

Summary

In summary, OTC products are available in the marketplace by two routes:

- OTC monographs, in which OTC drug products are based on categories of products; or
- New Drug Applications (NDAs).

The switch of a prescription drug to over-the-counter marketing requires a review of the post-marketing safety data and a determination that a consumer can adequately use the product in an OTC setting. Today's discussion will center on the NDA process, particularly as related to safety, efficacy and consumer's ability to understand and use these products in an OTC setting.