DATE: January 22, 2004

FROM: Center for Drug Evaluation and Research
Food and Drug Administration

SUBJECT: Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-related Gastrointestinal and Renal Toxicity

TO: State Boards of Pharmacy

The FDA is addressing this letter to bring to your attention important safety issues for all drug products that contain acetaminophen or NSAIDs. On September 19-20, 2002, the Nonprescription Drugs Advisory Committee, with experts from other committees, discussed available U.S. case report data regarding accidental and unintentional overdoses with acetaminophen and NSAID-related cases of gastrointestinal (GI) and renal toxicity.

This letter is intended to raise the awareness of pharmacists about the important educational role that they can play in preventing acetaminophen induced hepatotoxicity and NSAID-related gastrointestinal bleeding and renal toxicity in consumers using these medicines.

1. Acetaminophen Toxicity

The danger of hepatotoxicity in association with acetaminophen use has been well recognized. Acetaminophen induced hepatotoxicity is caused by a toxic metabolite of the parent compound and can lead to liver failure, which may result in liver transplant or death. The purpose of the advisory committee meeting was to review the data on unintentional overdose and determine whether additional measures should be taken to decrease the risk of these events.

Reasons for unintentional overdoses appear to be multi-factorial. Examples identified by the advisory committee included:

- The lack of consumer understanding of the potential adverse consequences of taking two different products containing acetaminophen simultaneously.
- Failure of consumers to recognize the potential harm from exceeding the recommended dose of medications.
- The wide variety of products available both OTC and by prescription that contain acetaminophen (e.g., combinations, single ingredient, multiple formulations).
- Failure of consumers to recognize the active ingredients in various combination prescription (Rx) and OTC drug products.
- Container labeling for prescription products, dispensed by a pharmacy, that may not clearly identify acetaminophen as one of the active ingredients and the maximum daily acetaminophen dose limit.

2. NSAID-related GI and Renal Toxicity

Multiple NSAIDs are available Over the Counter (OTC) (e.g., aspirin, ibuprofen, naproxen) and by prescription (ibuprofen, indomethacin, etc.). Attributable adverse events such as GI bleeding and renal toxicity associated with their use are well known. The following NSAID-related risk factors for GI bleeding were identified by the advisory committee:

- Use of concomitant medications such as anticoagulants, corticosteroids;
- concomitant use with low dose aspirin or with other NSAIDs;
- increasing age ($\geq$ 60 years);
- increasing dose;
- previous history of GI bleeding; and
- concomitant use of alcohol.

The following NSAID-related risk factors for renal toxicity were identified:

- Volume depletion;
- underlying kidney disease;
- congestive heart failure;
- elderly ($\geq$ 65 years);
- hypertension; and
- diabetes.

The advisory committee's discussions and suggestions about acetaminophen hepatotoxicity and NSAID-related GI and renal toxicity can be viewed on-line at the following FDA website:

http://www.fda.gov/ohrms/dockets/ac/cder02.htm#Nonprescription%20Drugs

The FDA believes that pharmacists are vital in any adverse event prevention effort. Pharmacists provide important information to patients and consumers regarding the appropriate use of prescription and OTC drug products. The Agency is asking that you consider the steps listed below to help ensure that patients and consumers use prescription and OTC pain relievers correctly. The following container labeling recommendations for prescription products are being submitted for your consideration:

Acetaminophen:

All prescription drugs containing acetaminophen should be adequately labeled on the container, so that all active ingredients (such as acetaminophen) and strengths appear on the prescription label. Additional recommendations for container labeling are as follows:

- Do not use drug name abbreviations, such as APAP for acetaminophen, to avoid consumer confusion.
- Include a statement instructing the patient to avoid concurrent use of any other acetaminophen containing products.
- Include a statement instructing the patient not to exceed the maximum daily recommended dose of acetaminophen.
- Include a statement instructing the patient to avoid alcoholic drinks while using the drug product.

NSAIDs:
We recommend that the labeling for all prescription products containing NSAIDs:

- Clearly identify that one of the ingredients in the product is an NSAID.
- Include a statement instructing the patient not to exceed the recommended single and/or daily dose.
- Include a statement instructing the patient to avoid taking any other NSAID containing products (OTC or Rx), or with products containing anticoagulants, corticosteroids, or diuretics.
- Include a statement instructing the patient to avoid alcoholic drinks while using the drug product.

FDA is reviewing various proposed changes to labeling for OTC products that contain acetaminophen and NSAIDs that will better reflect the latest scientific knowledge about the potentially serious risks associated with the use of these products. In the meantime, the FDA is planning a national educational campaign to alert U.S. consumers about the risks associated with the use of pain relievers and steps they can take to reduce these risks.

State Boards of Pharmacy regulate container labeling for prescription drugs. At present there are approximately two hundred approved new and generic combination narcotic analgesic prescription drug products that contain acetaminophen. Your assistance in addressing the container labeling requirements of prescription products that contain acetaminophen, as well as your assistance with education for both healthcare providers and consumers is essential for improving the safe use of analgesic/antipyretic drug products.

Thank you for your critically important contribution to the safety of patients taking acetaminophen and NSAID containing products.

Should you have any questions regarding this communication, please contact Dr. Charles Ganley, Director, Division of Over-the Counter Drug Products, 301-827-2222.

Sincerely,

Steven Galson, M.D., MPH
Acting Director
Center for Drug Evaluation and Research