



American Pain Foundation

**AMERICAN PAIN FOUNDATION SHARES ACETAMINOPHEN TASK FORCE'S CONCERNS
OVER RECENT FDA ADVISORY COMMITTEE RECOMMENDATIONS REGARDING
PRESCRIPTION ACETAMINOPHEN/OPIOID COMBINATION**

Background

On June 29 and 30, 2009, the United States Food and Drug Administration (FDA) held an Advisory Committee meeting regarding liver injury related to acetaminophen use in both over-the-counter (OTC) and prescription medicines. The Advisory Committee voted in favor of a number of potential changes¹, which will have far-reaching implications for Americans in pain and those providing their care. These include:

- reduction of the maximum recommended daily dose of acetaminophen
- reduction of the maximum recommended single dose of acetaminophen
- elimination of prescription acetaminophen/opioid combination medications

Of great concern was the lack of scientific evidence presented to support the recommendations made by the Advisory Committee. The briefing documents were less than robust and several panel members commented on insufficient data. Specifically, Dr. Judith Kramer, Advisory Committee member, stated "It seems to me that we were limited a lot today by lack of information about effectiveness -- dose-ranging information about effectiveness of acetaminophen for mild to moderate pain. And I think the agency and independent agencies, like the NIH and academics, should be encouraged to do studies, including 325, 500, 600 and 1,000, for the types of pain that are -- that these products are actually used for in practice"². Another Advisory Committee member, Dr. Knox Todd, stated that "I know those of us on the committee have felt a little whip-sawed about some of this information, and it's always difficult to -- to attempt to advise on policy in the lack of complete information"³. Recommendations made without full consideration of what is known about acetaminophen's potential for liver injury is dangerous considering unintended consequences of the proposed actions.

In response to the recent Advisory Committee recommendations, the Pain Care Forum⁴ has formed an Acetaminophen Task Force composed of its members and other stakeholders regarding liver injury related to acetaminophen.

It is the intent of this Task Force to communicate the concerns about the Committee's recommendations to the FDA through submissions to the docket by all interested stakeholders. The docket will close for submissions on September 30, 2009. This document is intended to provide an overview of the issues related to the recommendations regarding the prescription acetaminophen/opioid combination medications.

Implications of Eliminating Prescription Acetaminophen/Opioid Combination Medications

The potential consequences of the removal of prescription acetaminophen/opioid combination medications and the implications are detailed below.

- Elimination of prescription acetaminophen/opioid combination medications would remove effective medication options for healthcare practitioners treating patients with pain at the same time that significant constraints on prescribing of opioids are also being considered or implemented (e.g., REMS for immediate-release fentanyl for breakthrough pain, REMS under development for the extended release and long-acting opioid medications). The implication is:
 - The multiple regulatory actions currently being considered regarding prescription pain medications (both acetaminophen/opioid combinations and extended release opioids) will impact collectively on the medical profession and patients, which could exacerbate the existing problem of undertreatment of pain. Their impacts must be considered as a whole and not as isolated decisions.
- The removal of prescription acetaminophen/opioid combination medications from the market would leave few options for the treatment of moderate to moderately-severe pain, essentially forcing prescribers to choose among prescription non-steroidal anti-inflammatory drugs (NSAIDs), less effective medications (e.g. tramadol, propoxyphene), or potent single-agent opioids (which are Schedule II). The implications are:
 - If the use of prescription NSAIDs increased, cases of NSAID toxicity would be predicted to increase. NSAID toxicity, especially in the chronic setting but also when used acutely according to accepted dosing, has been associated with gastrointestinal bleeding, cardiovascular thrombotic events, renal toxicity, anaphylactic reactions as well as hepatic toxicity. It is unlikely, then, that an overall reduction in harm to patients would occur, but simply a shift in the types of adverse events. There is no clear evidence that the prescription combination acetaminophen/opioid medications, when used appropriately, cause liver toxicity.
 - If the Schedule III acetaminophen/opioid combination medications are no longer available, prescribers may decide to use medications that are less effective than acetaminophen/hydrocodone medications rather than prescribing a Schedule II medication, which would potentially result in less effective pain relief for patients.
 - If prescribers do choose to substitute the Schedule II opioid medications, restrictions on the prescribing of Schedule II medications (e.g., cannot phone in prescription to pharmacy or write for refills) will place a greater burden on patients and prescribers and potentially increase healthcare costs.
 - The rates of abuse, misuse and diversion for these Schedule II opioid medications would likely increase if rates of prescribing increase, which would not decrease the risks to public health compared to use of the acetaminophen combination medications.

- Hydrocodone is currently only available in combination with acetaminophen. Therefore, the elimination of combination medications would completely remove this medication for use by patients and automatically place any new single entity hydrocodone products in Schedule II.
- Removing acetaminophen/opioid combination products from the market will potentially increase the prescribing single entity Schedule II opioids, which have a higher rate of abuse than the combination medications. This could result in exacerbation of the current problem of prescription opioid abuse since no REMS is currently being proposed for immediate release single entity opioids.

Recommendations for Alternative Actions to Address Health Concerns

The cautions noted above are not intended to discount the health implications of inappropriate acetaminophen use but rather to raise important concerns that should be considered before any decisions are made. To that end, we offer the following recommendations as alternative options for addressing the health concerns of acetaminophen use without the complete elimination of the prescription combination medications.

- Changes in prescription acetaminophen/opioid combination medication labeling
 - Clearly indicating that the product contains acetaminophen (i.e., eliminate use of the term “APAP” as has recently been done for OTC medications) and that severe liver injury can result from inappropriate or overuse of acetaminophen.
 - Standardize labels on all medications containing acetaminophen to include a clearly understood and standardized icon or pictograph conveying both the ingredient (i.e., acetaminophen) as well as daily limits on use.
- Development and implementation of targeted education campaigns directed at both consumers and healthcare providers. Both consumer and healthcare provider campaigns should be delivered through various channels to maximize reach. The campaigns would introduce the icon/pictograph as well as presenting the risks of acetaminophen use. Both campaigns should be developed through testing of messages and their comprehension by the appropriate target audiences and evaluated after implementation for effectiveness. Ongoing awareness can only be achieved with adequate reach of the messages.

¹ [Questions and Vote Results for the June 29-30, 2009 Joint Meeting of the Drug Safety and Risk Management Advisory Committee with the Anesthetic and Life Support Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee.](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM170188.pdf)
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM170188.pdf>

² Meeting Transcript for the June 30, 2009 Joint Meeting of the Drug Safety and Risk Management Advisory Committee with the Anesthetic and Life Support Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM174699.pdf>

³ Meeting Transcript (for full citation, see note 2).

⁴ The Pain Care Forum is a group of over 50 organizations---professional associations, consumer organizations, industry members and others---which focuses on pain policy issues. It was founded in 2004 by the American Pain Foundation and other organizations to combat the fragmentation of knowledge and effort that exists in the pain community. Its goals are to provide a forum for the exchange of information and ideas about pain policy and legislation and support collaborative actions on common issues of concern.