CHPA

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August 26, 2009

Ms. Arlene Solbeck
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Bldg. 22, MS 5411
Silver Spring, MD 20993

Re: Request for agency exercise of enforcement discretion on a phrase within 21 CFR 201.326(a)(1)(iii)(A) and (v)(A), as promulgated in "Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Rule;" 74 Fed. Reg. 19385 (April 29, 2009) [Docket No. FDA-1977-N-0013]

Dear Ms. Solbeck:

In the above-referenced Federal Register notice, the agency issued a final rule to require new organ-specific warnings and related labeling for over-the-counter (OTC) internal analgesics, including those containing acetaminophen. Included in the rule was a requirement that products labeled for adults include the following warning:

"**Liver warning:** This product contains acetaminophen. Severe liver damage may occur if you take

• more than [insert maximum number of daily dosage units] in 24 hours, *which is the maximum daily amount*" [See 21 CFR 201.326(a)(1)(iii)(A) and 21 CFR 201.326(a)(v)(A), (italics and underlining added).]

The underlined language presents an issue for multi-ingredient combination products which contain less than the maximum single dose of acetaminophen. As written, for these products, the resulting labeling may be inaccurate and potentially confusing to consumers. CHPA requests that the agency exercise its enforcement discretion and not take enforcement action against manufacturers of OTC acetaminophen-containing combination medicines who choose to take one of two actions: (1) Either *delete* the italicized, underlined language, or (2) *add* the words "of this product" following the italicized, underlined language where the phrase as otherwise written inaccurately describes the maximum daily amount of *acetaminophen* in the product, but where the maximum number of daily dosage units referenced on the label is otherwise accurate for that particular medicine.

Under FDA's tentative final monograph for OTC internal analgesics, the maximum daily amount of acetaminophen is 4 grams. For OTC single ingredient products containing acetaminophen, arriving at the maximum number of daily dosage units is easy and accurate: 8- 500 mg tablets, 12- 325 mg tablets (which is actually 3.9 grams, but 13 tablets exceeds the maximum, so

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the intent is clear), etc. For OTC combination products which contain the maximum single dose of acetaminophen, arriving at the maximum number of daily dosage units is similarly easy and accurate: 4- 1000 mg packets, 8- 500 mg tablets, etc. However, for OTC combination products which contain less than the maximum single dose of acetaminophen, the maximum number of daily dosage units to be taken under labeled directions for that particular product in a 24 hour period can yield considerably *less* than the maximum daily amount of acetaminophen. Because the phrase "which is the maximum daily amount" refers back to acetaminophen in the liver warning, this means that, taken at its most literal, the phrase "which is the maximum daily amount" is not accurate. For example, the maximum daily dose on the label for the analgesic combination of acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg is 8 tablets in 24 hours. In this example, the daily amount of acetaminophen would be 2 g, which is obviously not the "maximum daily amount" of acetaminophen.

As a second example, a multiple symptom cold product in a dissolving powder could contain the maximum single doses of a nasal decongestant and an antihistamine, but less than the maximum single dose of acetaminophen. As with the acetaminophen-aspirin-caffeine example, the maximum daily dose for this product would be triggered by factors other than acetaminophen. In this example, it would be triggered by the nasal decongestant and antihistamine.

We did not raise this issue at the time of the December 2006 proposed rule because the phrase "which is the maximum daily amount" was not included in the liver warning in the proposal. See 71 Fed. Reg. 77333 (December 26, 2006). At the time of the proposed rule and continuing today, we fully agree with the concept behind the warning, ie, do not take more than directed on the label, but we did not envision a literal calculation of the tentative final monograph's 4 g daily maximum dose of acetaminophen being included in the phrasing of the liver warning.

We understand the agency intends to issue a notice in the Federal Register to amend this warning language. Until such time, we respectfully request that the agency write us in response to this letter, stating the agency's intentions on the exercise of enforcement discretion where manufacturers of OTC acetaminophen-containing combination medicines choose to modify the language to discourage overdosing, while, at the same time, being truthful, and not misleading. Actions could include either delete the phrase "which is the maximum daily amount" or add the words "of this product" following the phrase under 21 CFR 201.326(a)(1)(iii)(A) and (v)(A) where the phrase inaccurately describes the maximum daily amount of *acetaminophen* in the product, but where the maximum number of daily dosage units referenced on the label is otherwise accurate for that particular medicine.

Sincerely,

Barbara A. Kochanowski

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Vice President, Regulatory Affairs

cc: Michael S. Furness, Ph.D., Director, DNRD, Office of Nonprescription Products
Matthew R. Holman, Ph.D., Deputy Director, DNRD, Office of Nonprescription Products