

Submitted by the
CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

BRIEFING BOOK

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

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BRIEFING BOOK

Meeting of the Nonprescription Drug Advisory Committee DATE: 4 April 2017

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A. Introduction

On March 3, 2017, the U.S. Food and Drug Administration (FDA) announced a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)¹ to discuss safety issues associated with over-the-counter (OTC) analgesic combination products used for upset stomach (*i.e.*, heartburn, nausea, fullness, belching, gas, acid indigestion, and/or sour stomach) and hangover indications under the Internal Analgesic and Antacid monographs. It is important to note the safety of the combination of ingredients in these products, and not the individual ingredients, is the subject of this meeting. The Committees will also be asked to discuss the hangover indication under the Overindulgence, Internal Analgesic, and Stimulant Monographs.

Consumer Healthcare Products Association (“CHPA”) is the leading national trade association representing manufacturers and distributors of OTC drugs and dietary supplements. CHPA members manufacture OTC analgesic/antacid combinations indicated for the relief of upset stomach when accompanied by pain (headache or body aches). CHPA is not aware of any marketed analgesic/antacid combination products indicated for hangover. One of our members (Rally Labs LLC) markets an analgesic/stimulant combination product indicated for hangover (Blowfish). CHPA is serving as the industry sponsor for the April 4, 2017 NDAC meeting.

CHPA has an interest and expertise in the subject matter of the Advisory Committee meeting and is providing background information for the committee to review prior to the meeting. In addition to this material, NDAC/DSaRM members will receive background information (briefing book) from Bayer HealthCare LLC (Bayer). This briefing book should be referenced for further information on specific OTC analgesic/antacid combinations indicated for the relief of upset stomach when accompanied by pain. At the meeting, NDAC/DSaRM members will hear presentations from Bayer, Rally Labs LLC and a renowned researcher in the field of hangover research who has published extensively on the topic.

The Advisory Committee will discuss the hangover indication under the Overindulgence, Internal Analgesic, and Stimulant monographs. Herein, we provide an overview of marketed products indicated for treatment of hangover symptoms, the regulatory history of “hangover” in the OTC

¹ [Fed. Reg. Vol 82 \(41\): pp. 12457-8; Mar. 3, 2017](#)

monograph, and discuss the familiarity of this term among both consumers and the medical community and how that is consistent with the definition used in the monograph proposed by FDA. CHPA has invited two experts to attend the meeting. Damaris Rohsenow, Ph.D., Brown University ([bio](#)) has studied the physiological effects of alcohol, including hangover, for more than 40 years and has contributed significantly to the understanding of hangover symptoms and their measurement. Jonathan Howland Ph.D., MPA, MPH, is the Director of Public Health and Injury Prevention at Boston University Medical Center ([bio](#)). He has also published extensively in the field of hangover research, including the effects of low-dose and residual alcohol on occupational and neurocognitive performance.

We look forward to participating in the Advisory Committee discussion of OTC analgesic combination products used for upset stomach (*i.e.*, heartburn, nausea, fullness, belching, gas, acid indigestion, and/or sour stomach) with pain (headache or body aches), and hangover indications under several monographs.

B. Over-the-Counter (OTC) Combination Products Covered by this Meeting

1. OTC Analgesic/Antacid Combinations Indicated for Treatment of Upset Stomach When Accompanied by Pain (headache or body aches)

a) Marketed Products

Upset stomach is a general term used to describe symptoms associated with gastric hyperacidity such as acid indigestion, heartburn, or sour stomach.² Antacid products are widely used to treat heartburn, sour stomach, acid indigestion, or upset stomach.

Combination products indicated to treat upset stomach when accompanied by pain (headache or body aches) typically combine antacid active ingredients (sodium bicarbonate, citric acid) that neutralize stomach acid, with a pain reliever such as aspirin (acetylsalicylic acid or ASA) a nonsteroidal anti-inflammatory drug (NSAID), in an effervescent tablet. When the effervescent tablets are dissolved in water, an antacid effect is produced by the formation of sodium citrate, which is formed along with carbon dioxide. The antacid provides relief of gastric hyperacidity by neutralizing stomach acid resulting in an increased pH of stomach contents. Antacids also aid in the control of gastroesophageal reflux by increasing intraesophageal pH and decreasing pepsin activity. Aspirin is well-established as a safe and effective OTC analgesic^{3,4} and has been used for over 100 years to treat pain symptoms. The recommended single dose of aspirin for adults is 325 to 1000 mg with a 4000 mg maximum daily limit.

CHPA is not aware of any marketed product containing acetaminophen in combination with an antacid active ingredient indicated for dual symptoms associated with stomach discomfort (heartburn, acid indigestion, sour/upset stomach) and pain (headaches, body aches).

Examples of analgesic/antacid combination products identified from a search of the National Institutes of Health Daily Med website⁵ are provided in the Table below. Note that none of these products make hangover claims.

² Fed. Reg. Vol 47 (169); Aug. 31, 1982 @38482

³ Edwards, J. *et al.*, Oral aspirin in postoperative pain: a quantitative systematic review. 1999, *Pain* 81(3): 289-297

⁴ Derry, S. and Woore, R. Single dose oral aspirin for acute postoperative pain in adults. 2012, *Cochrane Database Syst Rev*. doi: 10.1002/14651858.CD002067

⁵ <https://dailymed.nlm.nih.gov/dailymed/>

OTC Analgesic/Antacid Combinations Indicated for Treatment of Upset Stomach

Product	Manufacturer	Active Ingredients (mg/tablet)	Uses which include 'Upset stomach'	Dosage
Alka-Seltzer Original	Bayer	Anhydrous citric acid (1000) Aspirin (325) Sodium bicarbonate (1916)	upset stomach with headache from overindulgence in food or drink	Two tablets every 4 hours (adults/children over 12) Two tablets every 4 hours or as directed by a doctor (adults over 60)
Alka-Seltzer Lemon Lime	Bayer	Anhydrous citric acid (1000) Aspirin (325) Sodium bicarbonate (1700)	upset stomach with headache from overindulgence in food or drink	Two tablets every 4 hours (adults/children over 12) Two tablets every 4 hours or as directed by a doctor (adults over 60)
Alka-Seltzer Extra Strength	Bayer	Anhydrous citric acid (1000) Aspirin (500) Sodium bicarbonate (1985)	upset stomach with headache from overindulgence in food or drink	Two tablets every 6 hours (adults/children over 12) Two tablets every 6 hours or as directed by a doctor (adults over 60)
Bromo Seltzer	Tower Laboratories	Citric acid (1000) Aspirin (325) Sodium bicarbonate (1916)	upset stomach with headache from overindulgence in food or drink	Adults/children ≥ 12 years of age: 2 tablets every 4 hours ≥ 60 years: 2 tablets every 4 hours
Effervescent Antacid and Pain Relief (Cardinal Health)	Cardinal Health	Citric acid (1000) Aspirin (325) Sodium bicarbonate (1916)	upset stomach with headache from overindulgence in food or drink	Adults/children ≥ 12 years of age: 2 tablets every 4 hours ≥ 60 years: 2 tablets every 4 hours

<p>Effervescent Pain Relief</p>	<p>Major Pharmaceuticals</p>	<p>Citric acid (1000) Aspirin (325) Sodium bicarbonate (1916)</p>	<p>upset stomach with headache from overindulgence in food or drink</p>	<p>Adults/children \geq 12 years of age: 2 tablets every 4 hours \geq60 years: 2 tablets every 4 hours</p>
<p>Medique Medi Seltzer</p>	<p>Unifirst First Aid Corp</p>	<p>Citric acid (1000) Aspirin (325) Sodium bicarbonate (1916)</p>	<p>upset stomach with headache from overindulgence in food or drink</p>	<p>Adults/children \geq 12 years of age: 2 tablets every 4 hours \geq60 years: 2 tablets every 4 hours</p>

b) Regulatory History

FDA published a Final Monograph on Antacids in June 1974⁶ allowing combination of antacid ingredients with any generally recognized as safe and effective analgesic as long as “it is indicated for use solely for the concurrent symptoms involved, *e.g.*, headache and acid indigestion, and is marketed in a form intended for ingestion as a solution”. The agency amended the Antacid Final Monograph in August 1982 to permit antacids to be labeled for the relief of upset stomach associated with heartburn, sour stomach, and acid indigestion.⁷

In a 1988 Tentative Final Monograph,⁸ FDA proposed that acetaminophen or aspirin may be combined with any antacid active ingredient⁹ for the temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion and upset stomach associated with these symptoms. Aspirin-containing combinations are also allowed additional claims to treat (for example) minor aches and pains associated with a cold, sore throat, headache, or toothache.

c) Product Safety and Efficacy

In a June 2016 Drug Safety Communication, FDA noted a total of 41 cases of serious bleeding events reported with OTC products containing aspirin, sodium bicarbonate, and citric acid during the period of January 1, 1969 through August 13, 2014. Of note, the majority (88%) of subjects using the aspirin containing products appeared to have underlying conditions¹⁰ that put them at risk of developing serious bleeding events. In addition, for many of the cases (20/41) either no details were provided about the dosing regimen or the patient used the product inappropriately by taking more than the recommended dosage.

In 2009, a warning about the risk of serious bleeding was added to the labels of all OTC products that contain NSAIDs, including aspirin-containing antacid products. Eight cases of serious bleeding events associated with these products occurred after this warning was added.

⁶ Part 331 - Antacid Products for Over-the-Counter (OTC) Human Use Fed. Reg. Vol 39 (108); June 4, 1974

⁷ Fed. Reg. Vol 47 (169); Aug. 31, 1982

⁸ Internal Analgesic, Antipyretic, and Antirheumatic Drug products for over-the-Counter Human Use, Fed. Reg. Vol 53 (221) @46258; Nov 16, 1988

⁹ Antacid active ingredients are identified in Part 331.11; aluminum-; bicarbonate-; bismuth-; calcium-; citrate-; glycine; magnesium-; milk solids, dried; phosphate-; potassium-; sodium-; silicates; tartrate-

¹⁰ Risk factors included age >60 years; use of anticoagulants, steroids or NSAIDs; history of stomach ulcers; history of alcohol abuse

The Bayer briefing book should be referenced to provide further data supporting the safety and efficacy of aspirin/antacid combination products indicated for the treatment of gastrointestinal symptoms when accompanied by pain (headache or body aches).

2. OTC Analgesic\Stimulant Combination Products Indicated to Treat Hangover Symptoms

a) Marketed Products

OTC ingredients used to treat individual symptoms associated with a hangover are recognized as Category I (generally recognized as safe and effective, GRASE). These include antacids, stimulants, and internal analgesics. Combinations of these ingredients are marketed to treat symptoms associated with a hangover. While both antacid/analgesic and analgesic/stimulant combinations of Category I ingredients are recognized as safe and effective for hangovers, the only OTC products currently being marketed with a hangover indication are analgesic/stimulant combinations.

Drug Products Indicated to Treat Hangover Symptoms

Product	Manufacturer	Active Ingredient (mg/tablet)	Uses	Directions
Blowfish	Rally Labs	Aspirin (500) Caffeine (60)	<ul style="list-style-type: none"> • temporary relief of minor aches and pains associated with a hangover • helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover • temporary relief of headaches or body aches and pains alone 	<p>1 or 2 tablets every 6 hours, as needed, or as directed by a doctor. Do not exceed 8 tablets in 24 hours (adults/children over 12)</p> <p>1 or 2 tablets every 6 hours, as needed, or as directed by a doctor. Do not exceed 4 tablets in 24 hours (adults over 60) Children under 12 years – do not use</p>
First Aid Shot Therapy Hangover Relief	Fast Labs	Choline salicylate (870)* Caffeine (65)*	<ul style="list-style-type: none"> • temporary relief of minor aches and pains associated with a hangover • helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover • temporary relief of headaches or body aches and pains alone 	<p>Swallow the contents of one bottle Repeat every 4 hours while symptoms persist Do not take more than 6 bottles in 24 hours Children under 12 years do not use</p>

*Total amount of active ingredient contained in a single dose (40 mL liquid)

While there are many folk remedies proposed to treat the symptoms of a hangover,¹¹ there have been relatively few clinical investigations into these treatments. In addition, many products marketed as dietary supplements claim to treat hangover symptoms or to prevent the occurrence of a hangover. There is limited evidence for the efficacy of these products.¹² Regardless, these are not appropriate indications for dietary supplements and these products should be considered misbranded.¹³

In preparation for the Advisory Committee meeting, CHPA reviewed serious adverse events contained in the FDA Adverse Events Recording System (FAERS) associated with aspirin and caffeine combinations (*e.g.*, Blowfish) indicated for the treatment of hangover. A search of the FAERS database performed in February 2017 revealed no cases of serious adverse events reported for “Blowfish”, confirming the long-standing general recognition of the safety of the ingredients in this product for use in the treatment of hangover symptoms.

b) Hangover Definition/Symptom Measurement

Adverse symptoms occurring several hours after the consumption of excess alcohol is referred to as a “hangover.” These symptoms, which occur as the blood alcohol level falls, affect numerous body systems including the gastrointestinal, neurologic, and endocrine, and typically differ in severity according to the amount of alcohol intake. Specific symptoms include headache, tiredness, nausea, loss of appetite, thirst, concentration problems, dizziness, diarrhea and mood changes.^{14,15} Cognitive effects associated with the hangover state, including changes in mood¹⁶ and memory function^{17,18} have also been described.^{19,20,21,22,23}

¹¹ Verster, J, and Penning, R. Treatment and Prevention of Alcohol Hangover. 2010, *Curr Drug Abuse Rev* 3(2): 103-109.

¹² Pittler, M. *et al.*, Interventions for preventing or Treating Alcohol Hangover: Systematic Review of Randomised Controlled Trials. 2005, *BMJ* 331 (7531):1515-1518.

¹³ [FDA Warning Letter to Amerilab Technologies, Inc March 16, 2010](#)

¹⁴ Verster, J. *et al.*, The Alcohol Hangover Research Group Consensus Statement on Best Practice in Alcohol Hangover Research. 2010, *Curr. Drug Abuse Rev* 3(2): 116-126

¹⁵ Penning, R. *et al.*, Alcohol Hangover Symptoms and Their Contribution to the Overall Hangover Severity. 2012, *Alcohol Alcohol* 47(3): 248-252

¹⁶ McKinney, A. A Review of the Next Day Effects of Alcohol on Subjective Mood Ratings. 2010, *Curr Drug Abuse Rev* 3(2): 88-91.

¹⁷ Verster, J. *et al.*, Alcohol Hangover Effects on Memory Functioning and Vigilance Performance After an Evening of Binge Drinking. 2003, *Neuropsychopharm* 28(4): 740-745.

¹⁸ McKinney, A. and Coyle, K. Next Day Effects of a Normal Night’s Drinking on Memory and Psychomotor Performance. 2004, *Alcohol Alcohol* 39(6): 509-513.

¹⁹ Stephens, R. *et al.*, A review of the literature on the cognitive effects of alcohol hangover. 2008, *Alcohol Alcohol* 43 (2):163-170.

Validated tools exist for the measurement of hangover symptoms^{24,24,25,26,27} and dose-dependent effects are observed.^{14,28,29,30,31,32,33} The incidence of reported hangover symptoms in studies utilizing standardized breath alcohol concentrations (BrAC) of 0.09-0.15 g% is typically ~ 70-80%.^{21,32,34,35,36}

c) Regulatory History

FDA and the Advisory Review Panel on OTC Miscellaneous Internal Drug Products spent considerable time between 1982 and 1991 reviewing the data available, and determined that hangover was an appropriate indication that was well understood by consumers. As reflected in more recent scientific and related literature, nothing has changed since that time with respect to the common usage

²⁰ Ling, J. *et al.*, Cognitive and psychomotor performance during alcohol hangover. *Curr. Drug Abuse Rev* 2010, 3 (2):80-87.

²¹ Rohsenow, D. *et al.*, Intoxication with bourbon versus vodka: effects on hangover, sleep, and next-day neurocognitive performance in young adults. 2010, *Alcohol Clin. Exp. Res* 34 (3):509-518.

²² Stephens, R. *et al.*, A critical analysis of alcohol hangover research methodology for surveys or studies of effects on cognition. 2014, *Psychopharmacology (Berl)* 231 (11):2223-2236.

²³ Hogewoning, A. *et al.*, Characteristics of social drinkers with and without a hangover after heavy alcohol consumption. 2016, *Subst. Abuse Rehabil.* 7:161-167.

²⁴ Rohsenow, D. *et al.*, Effects of heavy drinking by maritime academy cadets on hangover, perceived sleep, and next-day ship power plant operation. 2006, *J. Stud. Alcohol* 67(3): 406-15.

²⁵ Rohsenow, D. *et al.*, The Acute Hangover Scale: A New Measure of Immediate Hangover Symptoms. 2007, *Addict. Behav.* 32(6): 1314-20.

²⁶ Hesse, M. *et al.*, Predictors of hangover during a week of heavy drinking on holiday. 2010, *Addiction* 2010, 105(3): 476-83.

²⁷ Howland, J. *et al.*, The incidence and severity of hangover the morning after moderate alcohol intoxication. 2008, *Addiction* 103(5): 758-65.

²⁸ Harburg, E. *et al.*, Psychosocial factors, alcohol use, and hangover signs among social drinkers: a reappraisal. 1993 *J Clin Epidemiol* 46(5):413-422.

²⁹ Sjaastad, O. and Bakketeig, L. Hangover headache: accompanying symptoms. Vågå study of headache epidemiology. 2004, *J Headache Pain* 5:224-229.

³⁰ Sjaastad, O. and Bakketeig, L. Hangover headache. Prevalence: Vågå study of headache epidemiology. 2004, *J Headache Pain* 5:181-187.

³¹ Finnigan, F. *et al.*, The effects of self-administered alcohol-induced 'hangover' in a naturalistic setting on psychomotor and cognitive performance and subjective state. 2005, *Addiction* 100 (11):1680-1689.

³² Piasecki, T. *et al.*, Hangover frequency and risk for alcohol use disorders: evidence from a longitudinal high-risk study. 2005, *J Abnorm. Psychol.* 114 (2):223-234.

³³ Piasecki, T. *et al.*, Hangover and risk for alcohol use disorders: existing evidence and potential mechanisms. 2010, *Curr. Drug Abuse Rev* 3(2): 92-102.

³⁴ Chapman, L. Experimental Induction of Hangovers. 1970 *Q. J. Stud. Alcohol* 5 Suppl 83-86.

³⁵ Howland, J. *et al.*, Hangover Predicts Residual Alcohol Effects on Psychomotor Vigilance the Morning After Intoxication. 2010, *J. Addict. Res. Ther.* 1(101):1-11.

³⁶ Rohsenow, D. *et al.*, Effects of caffeinated vs. non-caffeinated alcoholic beverage on next-day hangover incidence and severity, perceived sleep quality, and alertness. 2014, *Addict. Behav.* 39(1): 329-32.

and understanding of the term or appropriate use of the product category among either consumers or the medical community.

On October 1, 1982, FDA issued a Notice of Proposed Rulemaking, discussing the use of OTC drugs to treat hangover symptoms.^{37,38} “Hangover” was defined by the Expert Panel as “[a] *condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic systems that follows recent acute excessive alcohol ingestion. These symptoms may include nausea, heartburn, thirst, tremor, disturbance of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.*” OTC combination products initially proposed for the treatment of hangover symptoms encompassed active ingredients from at least two of the following three categories: analgesics,³⁹ antacids,⁴⁰ and stimulants.⁴¹

In December 1991, FDA proposed to establish conditions under which OTC drug products for relief of symptoms associated with overindulgence in food and drink (*e.g.*, upset stomach, hangover symptoms) would be generally recognized as safe and effective.⁴² Because active ingredients recommended for treatment of hangover symptoms consisted of combinations of ingredients already considered to be GRASE in other OTC drug monographs (Antacid, Internal Analgesic, Stimulant), FDA determined that a separate monograph for these active ingredients for relief of hangover symptoms was not needed. Instead, at that time, FDA proposed to amend the Final (or Tentative final) monographs for Antacid, Stimulant and Internal Analgesic drug products to incorporate indications for the relief of hangover symptoms. FDA reversed the Panel’s recommendation to allow any combination of two of more of these ingredients, and removed from Category I combination products

³⁷ Orally Administered Drug Products for Relief of Symptoms Associated With Overindulgence in Alcohol and Food for Over-the-Counter Human Use; Establishment of a Monograph. *Fed. Reg.* Vol 47 (191) @43543; Oct. 1, 1982

³⁸ FDA originally proposed establishing conditions for products intended to treat hangover on October 1, 1982 under the “Overindulgence in Alcohol and Food” OTC Monograph. The title of this monograph was changed to ‘Overindulgence in Food and Drink’ on December 24, 1991. At that time, FDA proposed to remove hangover indications from the Overindulgence monograph and instead amend the Final Monographs for Antacids (21 CFR Part 331) and Stimulants (21 CFR Part 340) and the Tentative Final Monograph for Internal Analgesics to include appropriate conditions for relief of hangover symptoms.

³⁹ Any analgesic active ingredient permitted in Part 343

⁴⁰ Any antacid active ingredient permitted in Part 331

⁴¹ Any stimulant active ingredient identified in Part 340

⁴² Orally Administered Drug Products for Relief of Symptoms Associated with Overindulgence in Food and Drink for Over-the-Counter Human Use, *Fed. Reg.* Vol 56 (247); Dec 24, 1991

containing both an antacid ingredient and caffeine,⁴³ based on evidence that caffeine stimulates gastric secretion of hydrochloric acid.⁴⁴ Subsequent data provided to FDA disputes this.⁴⁵

d) Consumer/Professional References to “Hangover”

The term “hangover” has been in use since at least 1904 and is found in common⁴⁶ and medical dictionaries.⁴⁷ FDA’s use of the term “hangover” as it is defined in the rulemaking is consistent with historical use and continues to be validated in common usage. Sources of medical information for consumers such as Mayo Clinic⁴⁸ and WebMD⁴⁹ organize information around the keyword “hangover”, as do government sources of information such as the NIH. It is a well-recognized condition as evidenced by the fact that there are thousands of articles on the topic.⁵⁰

Use of the term “hangover” is appropriate versus a lengthy list of possible symptoms, and is similar to cough/cold or upset stomach where one or more symptoms may be present and treated with a combination OTC product. In the case of hangover, a single term to refer to multiple symptoms is perhaps even more appropriate given that the condition is unambiguously related to one single, clearly identifiable cause (alcohol consumption).

⁴³ Orally Administered Drug Products for Relief of Symptoms Associated With Overindulgence in Food and Drink for Over-the-Counter Human Use; Tentative Final Monograph. *Fed. Reg.* Vol 56 (247) @66746; Dec. 24, 1991

⁴⁴ McArthur, K. *et al.*, Relative stimulatory effects of commonly ingested beverages on gastric acid secretion in humans, *Gastroenterology* 1982; 83: 199-203

⁴⁵ The docket contains two letters from medical experts in response to FDA’s position (letter from David J. Buddrus, M.D., dated April 10, 1992 and letter from Burde Kamanth, Ph.D., dated April 22, 1992) which closely examined the literature cited by FDA in the comments to the proposed monograph. Both experts take issue with the agency’s conclusion.

⁴⁶ <http://www.dictionary.com/browse/hangover>. Accessed on March 1, 2017.

⁴⁷ <http://www.medicinenet.com/script/main/art.asp?articlekey=26220>. Accessed on March 1, 2017.

⁴⁸ <http://www.mayoclinic.org/diseases-conditions/hangovers/basics/symptoms/con-20025464>. Accessed on March 1, 2017.

⁴⁹ <http://www.webmd.com/a-to-z-guides/common-topics/default.htm>. Accessed on March 1, 2017.

⁵⁰ As an example, a search on Google Scholar (performed March 6, 2017) for “alcohol hangover” yields approximately 28,200 results.

Based on numerous references to the term and the evidence of long-standing universal consumer understanding of the term, we strongly recommend continued use of hangover when referencing treatment of symptoms experienced after alcohol consumption, and believe that the hangover indication as proposed by the Expert Panel and FDA continues to be an appropriate part of the Internal Analgesic and Stimulant Monographs.