Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
April 4, 2017

Location: Tommy Douglas Conference Center
10000 New Hampshire Avenue, Silver Spring, Maryland 20903

Topic: The committees will discuss safety issues associated with over-the-counter 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 in 21 CFR part 343 and 21 CFR part 331, respectively. The committees will also be asked to discuss the hangover indication under the Overindulgence, Internal Analgesic, and Stimulant monographs in 21 CFR part 357 subpart J, 21 CFR part 343, and 21 CFR part 340, respectively.

These summary minutes for the April 4, 2017 joint meeting of the Nonprescription Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on July 5, 2017.

I certify that I attended the April 4, 2017 joint meeting of the Nonprescription Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Moon Hee V. Choi, PharmD
Designated Federal Officer, NDAC

/s/
Christianne L. Roumie, MD, MPH
Chairperson, NDAC

Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
April 4, 2017

The following is the final report of the joint meeting of the Nonprescription Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, held on April 4, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Division of Nonprescription Drug Products, the Office of Surveillance and Epidemiology, and posted on the FDA website at:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm544714.htm and
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm536632.htm.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Nonprescription Drugs Advisory Committee (NDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on April 4, 2017, at the Tommy Douglas Conference Center, 10000 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA, Consumer Healthcare Products Association and Bayer HealthCare LLC. The meeting was called to order by Christianne L. Roumie, MD, MPH (Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Designated Federal Officer). There were approximately 110 people in attendance. There were two Open Public Hearing (OPH) speaker presentations.

Issue: The committees discussed safety issues associated with over-the-counter 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 in 21 CFR part 343 and 21 CFR part 331, respectively. The committees were also be asked to discuss the hangover indication under the Overindulgence, Internal Analgesic, and Stimulant monographs in 21 CFR part 357 subpart J, 21 CFR part 343, and 21 CFR part 340, respectively.

Attendance:

NDAC Members Present (Voting): Elma D. Baron, MD; Janet P. Engle, PharmD, PhD (Hon), FAPhA, FCCP, FNAP; Neil J. Farber, MD, FACP; Tonya S. King, PhD; Paul Pisarik, MD, MPH, FAAFP; Christianne L. Roumie, MD, MPH (Chairperson); Lee M. Sanders, MD, MPH; W. Thomas Smith, PharmD, JD; Victor Wu, MD, MPH

NDAC Member Present (Non-Voting): Roger G. Berlin, MD, FACP, FACG (Industry Representative)

NDAC Member Not Present (Voting): Estela M. Pledge, MS, LCPC, MAC, ACS (Consumer Representative)

DSaRM Members Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Christopher H. Schmid, PhD; Andy S. Stergachis, PhD, BPharm; Linda Tyler, PharmD, FASHP; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

DSaRM Member Present (Non-Voting): Linda Scarazzini, MD, RPh (Industry Representative)

DSaRM Members Not Present (Voting): Tobias Gerhard, PhD, RPh; Suzanne B. Robotti (Consumer Representative); Anne-Michelle Ruha, MD, FACMT; Til Sturmer, MD, MPH, PhD; Almut Winterstein, RPh, PhD, FISPE

Temporary Members (Voting): Dawn Aldrich, MPH, PhD (Patient Representative); Timothy O. Lipman, MD; Richard A. Neill, MD; Steven Solga, MD; Marc D. Wishingrad, MD

FDA Participants (Non-Voting): Lesley-Anne Furlong, MD; Karen Mahoney, MD; Valerie Pratt, MD; Steven Adah, PhD; S. Christopher Jones, PharmD, MS, MPH

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers: Megan Polanin, PhD (National Center for Health Research); David Spangler (Consumer Healthcare Products Association)

The agenda was as follows:

Call to Order and Introduction of Committee	**Christianne L. Roumie, MD, MPH** Chairperson, NDAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, NDAC
FDA Introductory Remarks	**Valerie Pratt, MD** Deputy Director for Safety Division of Nonprescription Drug Products (DNDP) Office of Drug Evaluation IV (ODE IV) Office of New Drugs (OND), CDER, FDA

FDA PRESENTATION

Analgesic Combinations in the Over-the-Counter (OTC) Monographs	**Captain Mary Vienna, USPHS, Ret.** Interdisciplinary Scientist Reviewer DNDP, ODE IV, OND, CDER, FDA

INDUSTRY PRESENTATIONS	**Consumer Healthcare Products Association (CHPA)**
Introductory Remarks	**Barbara Kochanowski, PhD** CHPA
Alka-Seltzer Aspirin/Antacid Combination Products	**Andre Schmidt, MD** Bayer HealthCare LLC
Introduction to Hangover	**Jay Sirois, PhD** CHPA
Clinical Investigation of Hangover	**Damaris Rohsenow, PhD** Brown University (Consultant to CHPA)
OTC Products for Hangover Under the FDA Monograph	**Brenna Haysom** Rally Labs LLC
Summary	**Barbara Kochanowski, PhD**
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
Postmarketing Safety Data	**Ali Niak, MD** Medical Officer Division of Pharmacovigilance I Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology CDER, FDA
Selected Clinical Literature Overview	**Ketan Parikh, MD** Medical Officer DNDP, ODE IV, OND, CDER, FDA
Clarifying Questions	
LUNCH Open Public Hearing	
Charge to the Committee	**Valerie Pratt, MD**
Questions to the Committee/Committee Discussion	

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the safety of the use of over-the-counter (OTC) analgesic combination products for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea.

   Committee Discussion: *Committee members noted that aspirin is associated with ulcers over time, that erosive gastritis is a complication of NSAID use in general, and that the most common adverse effects for aspirin were gastrointestinal (GI), which raises the question about whether aspirin may decrease effectiveness in combinations labeled for GI indications. Several committee members noted that there would be safety issues associated with consumer misunderstanding of the product labeling where there may be confusion on the frequency of use, duration of use, and when to appropriately take the combination product, and that this confusion may lead to harmful effects. One committee member noted that the language of minor aches and pains associated with GI symptoms is confusing. Another committee member stated that brand extensions can be confusing, noting the number of different products carrying the Alka-Seltzer name but containing different active ingredients as an example. Also, another member expressed concern about the sodium load with effervescent products. One committee member stated that aspirin does not cause bleeding when used short term, but that it potentiates bleeding. Several committee members stated that although the combination product doesn't represent current best practice to treat the associated symptoms, they did not observe significant new safety concerns based on the data and the number of adverse events reported. Please see the transcript for details of the committee discussion.*

2. **VOTE**: Is the combination of an analgesic with antacids a rational combination for OTC use for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea?

   Vote Result: Yes: 5 No: 15 Abstain: 0

   Committee Discussion: *The majority of the committee voted "No," agreeing that the combination of an analgesic with antacids is not a rational combination for OTC use for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea. Some committee members who voted "No" added that use of a combination product containing these active ingredients for these gastric indications is contradictory (i.e., not helpful) and does not meet the required definition under the Combination Rule. Other committee members who voted "No" agreed that there are issues with the labeling that could lead to a lack of consumer understanding and confusion, and agreed that using a combination of an analgesic with antacids is not rational concurrent*

therapy. Some committee members who voted "Yes" stated that the data do not confirm that the presence of an analgesic product would decrease the efficacy of the antacid product when used in combination, and that short-term use of the combination product is not irrational. Please see the transcript for details of the committee discussion.

3. Hangover is defined in the monograph as a condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic system that follows recent acute and excessive alcohol ingestion. The monograph states that the symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.

   DISCUSSION: Discuss whether or not the treatment of hangover is an appropriate indication for OTC drug products. If the hangover indication is appropriate, which ingredients would be options for the treatment of the symptoms?

   We are particularly interested in a discussion of aspirin or acetaminophen as acceptable ingredients to include in combination products for the treatment of hangover. Consider in your discussion the indications for hangover in the monograph, the association of alcohol and NSAIDs with gastrointestinal bleeding, the association of alcohol and acetaminophen with liver toxicity, and the safety information presented in this meeting.

   ***Committee Discussion**: The opinion of the committee regarding whether or not the treatment of hangover is an appropriate indication for OTC drug products was mixed. Committee members expressed concern regarding the monograph's definition of hangover, which includes terms related to intoxication and alcohol abuse. Since hangover is a self-limited condition, it was not clear to the committee if treatment is necessary and if the current combination products have demonstrated efficacy for hangover per se. It was also unclear to the committee when consumers take these products in relation to alcohol use (the timing of use).*

   The committee thought labeling could be improved and questioned consumers' ability to comprehend the label, especially when they are hung-over. The majority of the committee agreed that more informative labeling is needed, and there may be an opportunity to better educate consumers, especially adolescents and young adults, of the risk of alcohol consumption. The committee advised that the label should not provide a false sense of security with regards to alcohol ingestion nor imply drugs ameliorate dangerous effects of alcohol on the body. The committee also commented that labeling how much time should elapse from the time of the last drink before taking these products may be helpful to consumers and pharmacists.

   The majority of the committee agreed that acetaminophen is not an appropriate ingredient to include in combination products for hangover due to its known risk of liver toxicity. The majority of the committee also agreed that use of products containing aspirin for hangover is less worrisome (than acetaminophen). One member asked if other NSAIDs could be used and another committee member stated that a monograph dose of caffeine is unlikely to be a problem. In summary, there was more concern expressed for use of acetaminophen than

aspirin to treat hangover. The committee also noted there were no efficacy data for the treatment in the hangover indication.

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 2:47 p.m.