FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE (NDAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Tuesday, April 4, 2017

7:59 a.m. to 2:48 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. ROUMIE: Good morning. I want to welcome everyone. This is a CDER meeting, C-D-E-R. If you are here for CBER, C-B-E-R, you are next door. Just making sure everybody's in the right place.

Good morning. First, I'd like to remind everyone to silence their cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Andrea Fischer. If you are present --

My name is Christianne Roumie. I'm the chairperson of the Nonprescription Drugs Advisory Council. I will be chairing the meeting. I will now call the joint Nonprescription Advisory Committee and Drug Safety Risk Management Advisory Committee meeting to order.

We'll start by going around the table and introducing ourselves. We will start on my right.

DR. NEILL: Good morning. I'm Richard Neill, family physician from the University of Pennsylvania on the NDAC.

DR. BARON: Good morning. I'm Elma Baron, professor at University Hospitals, Case Western Reserve University.

DR. SANDERS: Hi. I'm Lee Sanders, pediatrician from Stanford University.

DR. PISARIK: I'm Paul Pisarik, family physician, St. John Health Systems in Tulsa, Oklahoma.

DR. WU: Good morning. Victor Wu, internal medicine physician from the Bureau of Tennessee's Healthcare Finance Administration.

DR. BESCO: Good morning, everyone. My name is Kelly Besco. I'm the medication safety officer for the OhioHealth Hospital System in Columbus, Ohio, and I'm a member of the Drug Safety and Risk Management Committee.

DR. STERGACHIS: Andy Stergachis, professor of pharmacy and global health, University of Washington, a member of DSaRM.

DR. CHOUDHRY: Good morning. Niteesh Choudhry. I'm an internist and professor of Harvard Medical School and also a member of DSaRM.

DR. FARBER: Good morning. I'm Neil Farber, professor of clinical medicine and internal medicine at University of California, San Diego, and I'm on NDAC.

DR. ALDRICH: Good morning. I'm Dawn Aldrich, and I'm from SOLUTIONS Cancer Resource Center. That's in New York.

DR. SMITH: Hello. Tommy Smith, associate dean, Manchester University College of Natural Pharmacy and Health Sciences.

DR. SCARAZZINI: Hi. Good morning. Linda Scarazzini. I'm the head of pharmacovigilance and patient safety at AbbVie and the industry rep on DSaRM.

DR. BERLIN: Good morning. I'm Roger Berlin. I'm principal at 1.618 Consulting, and I'm the IR for NDAC. Good morning. Thanks.

DR. FURLONG: Good morning. My name is Lesley Furlong. I'm the deputy office director in

the Office of Drug Evaluation IV at CDER, FDA.

DR. MAHONEY: Karen Mahoney, deputy director, Division of Nonprescription Drug Products, FDA.

DR. PRATT: Valerie Pratt, deputy director for safety in the Division of Nonprescription Drug Products, FDA.

DR. ADAH: Steven Adah, interdisciplinary scientist team lead, Division of Nonprescription Drug Products, FDA.

DR. JONES: Hello. My name is Chris Jones. I'm the director of the Division of Pharmacovigilance, Office of Surveillance and Epidemiology at FDA.

DR. SCHMID: Chris Schmid. I'm a professor of biostatistics at Brown, and I'm on DSaRM.

DR. LIPMAN: Tim Lipman. I'm a gastroenterologist. I'm retired chief of the local Washington, DC VA Medical Center, ad locum. Thank you.

DR. WISHINGRAD: Marc Wishingrad, gastroenterologist in Los Angeles.

DR. SOLGA: Steve Solga, transplant hepatologist at the University of Pennsylvania.

DR. WARHOLAK: I'm Terri Warholak. I'm an associate professor at the University of Arizona College of Pharmacy. I'm in health outcomes.

DR. TYLER: I'm Linda Tyler. I'm the chief pharmacy officer at University of Utah Hospitals and Clinics and serve as associate dean at College of Pharmacy. I'm on DSaRM.

DR. ENGLE: Good morning. Jan Engle. I'm a pharmacist, professor, and head of the Department of Pharmacy Practice at University of Illinois at Chicago College of Pharmacy, and I'm on NDAC.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. ROUMIE: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now, I will pass to Moon Hee Choi, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's joint meeting of the

Nonprescription Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and temporary voting members of these committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special

government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services, which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and for the purposes of 18 U.S.C., Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of safety issues associated with the 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.

This is a particular matters meeting during which general matters will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they

have made concerning the topic at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Linda Scarazzini and Roger Berlin are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Scarazzini is employed by AbbVie, and Dr. Berlin is an independent consultant.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committees of any financial relationships that they might have regarding the topic that could be affected by the committees'

discussions. Thank you.

DR. ROUMIE: Thank you. We will now proceed with the FDA's opening remarks from Dr. Valerie Pratt.

FDA Introductory Remarks – Valerie Pratt

DR. PRATT: Good morning, Dr. Roumie, members of the Nonprescription Drugs Advisory Committee, and Drug Safety and Risk Management Advisory Committee, guest members, industry representatives, and members of the public.

My name is Valerie Pratt. I'm the deputy director for safety in the Division of Nonprescription Drug Products. On behalf of the division and all of us at FDA, it is my pleasure to welcome you to the Washington area.

Before we get started, I want to thank the members of the advisory committees who have taken time out of their busy schedules to thoughtfully review the briefing packages and to be here today. Although this is a joint NDAC and DSaRM meeting, we also have a number of guest members supplementing our committee. As members of the advisory

committee, you provide important expert scientific advice that is taken very seriously by the FDA.

Last but certainly not least, I would like to thank those members of the public, including representatives from various professional societies and the consumer groups who have taken the effort to be here today, to present your views or have provided written feedback. Your input is extremely valuable both to the committee in their deliberations and to the FDA.

Today, we're here to discuss safety issues associated with over-the-counter or OTC analgesic combination products used for upset stomach and hangover indications under the internal analgesic and antacid monographs, as well as to discuss the hangover indication under the overindulgence, internal analgesic and stimulant monographs. For those of you who are unfamiliar with the monograph, the next speaker will provide an explanation of the rulemaking process.

The analgesics permitted in combination with other active ingredients for these indications are

aspirin and acetaminophen. Please note that our focus today is combination products for these indications, not the use of single ingredient, aspirin, acetaminophen, or bismuth subsalicylate for other indications.

Antacid analgesic drug products containing aspirin or acetaminophen are currently allowed to be marketed under the OTC monograph for the temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion, upset stomach associated with overindulgence in food and drink, and symptoms related to hangover.

The safety of antacid/aspirin products for the relief of gastrointestinal symptoms has been discussed throughout the rulemaking process. Bleeding is a known risk of aspirin therapy because aspirin reduces cytoprotection of the GI mucosa due to dose-dependent impairment of prostaglandin E2 synthesis, and it decreases platelet aggregation due to irreversible inhibition of thromboxane A2 production.

21 CFR 330.10(a)(4)(iv) stipulates when an

OTC drug may combine two or more safe and effective active ingredients, one of the requirements is that the combination provide rational, concurrent therapy for the target population.

You will be hearing more about panels of external experts, called advisory panels, who helped FDA in the early years of the OTC monograph from our next speaker.

We note here only that the Antacid Advisory Panel and the Internal Analgesics Panel reached different conclusions regarding the safety and labeling of these products. In addressing these concerns, the FDA limited the dosage form of aspirin/antacid products to oral solutions since the only safety data available at the time were for that dosage form, and deferred to labeling as a means to ensure proper use of the drug.

On the other hand, OTC monograph allows antacid/acetaminophen products to be either solutions or solid oral dosage forms. However, concern for an association between major bleeding events and use of aspirin/antacid products persist.

Accordingly, FDA issued a drug safety communication in June 2016, which stated the agency plan to convene an advisory committee to address this concern.

On December 24, 1991, a tentative final monograph, or TFM, was published that amended the antacid and internal analgesics monograph to add indications for antacid and antacid/analgesic combination drug products. These amendments were part of a larger effort to establish a separate monograph for overindulgence, which allotted appropriate indications related to relief of such symptoms to the related monograph categories.

As a result of this effort, antacid added the indication, overindulgence in food and drink. The antacid/analgesic combination products added the indication, overindulgence in food and drink and hangover relief. And the analgesic/caffeine combination products added the indication, hangover relief.

Regarding hangover, the panel concluded that no clinical studies were necessary to demonstrate

effectiveness in treating hangover because it includes a variety of signs and symptoms that vary in frequency and severity between individuals and each episode.

In 2009, the organ-specific warnings final monograph included new labeling requirements for acetaminophen, which included warnings to highlight the potential for hepatotoxicity, which is also associated with alcohol use.

Alcohol use may induce changes in cytochrome P450 CYP2E1 levels, which may result in more acetaminophen metabolized to the reactive metabolite, N-acetyl-p-benzoquinoneimine or NAPQI. Alcohol also suppresses hepatic glutathione production, further increasing the risk of liver injury since glutathione binds NAPQI leading to the renal excretion of mercapturic acid.

In 1991, the overindulgence tentative final monograph permits the sale of antacid/analgesic products for indications, including upset stomach associated with hangover. The tentative final monograph also proposed the analgesic/caffeine drug

product, for the temporary relief of minor aches and pains associated with hangover, helps to restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover.

Although no analgesic-antacid products containing acetaminophen were identified in the current analysis, products containing acetaminophen/caffeine were, and the agency is concerned that the current monograph structure permits the sale of products containing acetaminophen for indications related to hangover.

Due to the lengthy history of the monograph and its resulting complex nature, the issues discussed here today touch upon four separate monographs: the internal analgesic, antacid, overindulgence, and stimulant monographs. And then it's true these monographs are part of larger effort to establish a separate monograph for overindulgence in 1991.

As a result, the issues of upset stomach and hangover are interwoven. One cannot address one

without affecting the other.

Given the advances in science in the past 26 years regarding the use of analgesics, the agency determined that an advisory committee is needed to reconsider the safety of certain combinations that can be marketed under these monographs that affect the health of Americans.

Thank you again for your participation in today's meeting. We look forward to a productive and thoughtful day. Interdisciplinary scientist, Captain Vienna, will now present analgesic combinations in the over-the-counter monograph.

DR. ROUMIE: Thank you, Dr. Pratt.

Before Dr. Vienna, can Dr. King introduce herself?

DR. KING: Yes. I am Tonya King, professor of biostatistics at Penn State University College of Medicine. Thank you.

DR. ROUMIE: Thank you. Captain Mary Vienna will now start with the FDA presentation on analgesic combinations in over-the-counter monographs.

FDA Presentation - Mary Vienna

CAPT VIENNA: Good morning. My name is Mary Vienna, and today I'm going to discuss the history of the analgesic combination drug products in the over-the-counter monograph regulatory system.

I'm going to briefly discuss the monograph process itself for those new to the topic. I'll discuss analgesic combinations, primarily antacid/analgesic drug products and the various monographs in which they appear. I'll discuss the labeling experience in terms and indications and safety warnings of concern for the combination products.

A monograph is an FDA regulation that serves as a rule book for formulating an OTC product by specifying conditions of use under which a drug product is considered generally recognized as safe and effective, or GRASE. These conditions include active ingredients, allowed concentrations, dosage forms, labeling, and other requirements such as drug registration and listing, current good manufacturing practices, and applicable labeling

regulations. Drugs that meet these standards can be marketed without FDA review.

The OTC monograph process was established in response to the 1962 Harris-Kefauver amendment to the Food, Drug, and Cosmetic Act, which requires drugs to demonstrate efficacy.

The FDA needed to evaluate the estimated 100,000 to half a million OTC drugs that were currently on the market, so in response, they established the OTC Drug Review in which they assigned active ingredients to therapeutic categories, then formed advisory review panels, which are different from the advisory committees of today.

These panels were comprised of scientists and clinicians who conducted reviews of literature and data submitted by industry for the active ingredients of a particular therapeutic category, and then recommended a list of active ingredients and conditions of use that they determine to be GRASE, or safe and effective, for the FDA to review.

In evaluating active ingredients and potential combinations, the advisory panels considered them within the framework of the OTC Combination Rule, a regulation published in 1973 that states, "An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect, when combining does not decrease the safety or effectiveness of any of the individual active ingredients, and when the combination, when used under adequate directions for use and warnings against unsafe use, provides a rational concurrent therapy for a significant proportion of the target population."

The development of a monograph is a lengthy, multistep, public rulemaking process, and the results of each phase are published in the Federal Register. The Advisory Review Panel's recommendations are published as an advance notice of proposed rulemaking, or ANPR, with the request for data and public comments. Comments can be

submitted by the drug industry, medical professionals, scientists, consumer advocates, and the general public.

FDA considers the comments received, evaluates any additional data submitted, revises the ANPR as appropriate, and publishes the revision as a proposed rule, or PR. The publication of the proposed rule, also known as the tentative final monograph, or TFM, is followed by another round of public comment and subsequent evaluation by the FDA of comments and data.

The final rule, or final monograph, is then published in the Federal Register and also establishes a regulation in the Code of Federal Regulations known by the acronym, CFR.

The antacid monograph is the first place you see the concept of an antacid/analgesic combination. The recommendations of the Antacid Advisory Panel was published on April 5, 1973. The panel reviewed antacid ingredients such as calcium carbonate and magnesium hydroxide and did not consider other acid-reducing agents such as H2

blockers or proton pump inhibitors. The panel concluded it was rational to combine an antacid with an analgesic for concurrent symptoms.

After consideration of comments and data submitted by the public, the FDA published the tentative final monograph on November 12, 1973 and addressed a number of comments that contended that the antacid/aspirin combination is unsafe for individuals with gastric complaints.

The FDA agreed that the combination should not be used by patients with gastric disease, except on the advice of the physician, and concluded that labeling would be sufficient to ensure proper use.

On June 4, 1974, the FDA published the final monograph. In response to additional comments that question the safety of antacid/aspirin combination products for treatment of GI symptoms, the FDA amended the monograph to limit combination products to dosage forms intended for ingestion as a solution, as all data available were derived from studies and experience with products in solution.

The FDA noted safety, effectiveness, and appropriate labeling of this specific analgesic component remained under review by the Internal Analgesic Panel, and the antacid final monograph is codified in 21 CFR, part 331.

Three years later, the recommendations of the Internal Analgesic Advisory Panel was published as an ANPR on July 8, 1977. In contrast to the Antacid Advisory Panel, the Analgesic Advisory Panel recommended that only acetaminophen be combined with antacid ingredients for the relief of concurrent symptoms, as aspirin combined with antacid ingredients, regardless of the antacid strength, should be labeled for analgesic indications only.

The panel found it irrational to provide claims for an antacid effect since aspirin may potentiate peptic ulcer, stomach distress, or heart burn. The FDA acknowledged the disparity between the antacid final monograph and the Antacid Advisory Panel's recommendations reflected there and the difference between the Internal Analgesic

Advisory Panel's recommendations and sought comment.

On November 16, 1988, the FDA published the tentative final monograph for the internal analgesics. The rule proposed only aspirin and acetaminophen as safe and effective ingredients for the antacid/analgesic combinations.

In response to comments regarding an antacid relief claim for antacid/aspirin products, the FDA allowed the claim but limited that combination to dosage forms intended for ingestion as a solution because the FDA did not receive data showing the combination in solution presents the risk of massive GI hemorrhage in normal individuals. However, the agency proposed no restrictions on oral dosage forms for acetaminophen-antacid combination products, as acetaminophen does not have the same GI effects.

FDA also concluded that it was necessary to provide consumers with the aspirin label warning, "Do not take this product if you have stomach problems such as heartburn, upset stomach, or

stomach pain that persists or recur, or if you have ulcers or bleeding problems, unless directed by a doctor."

Over time, the indications for antacids expanded under a variety of rulemakings. The antacid final monograph published in 1974 established the indications for heartburn, sour stomach, and/or acid indigestion. In 1982, the final monograph was amended to add in upset stomach indication as a term used by consumers to describe symptoms of gastric hyperacidity. These are the indications for the combinations codified at 21 CFR 331.15(b).

In 1991, a tentative final monograph was published to add the indication, upset stomach due to overindulgence in food and drink with associated symptoms of heartburn, nausea, and fullness, with the symptoms, belching and gas, added in 2005.

The 1991 tentative final monograph also added the indication, upset stomach associated with a hangover. These latter two indications were part of a larger effort to establish a separate

monograph for the therapeutic category of overindulgence.

The overindulgence monograph was published as a tentative final monograph on October 1, 1982 and reflected the recommendations of the Advisory Review Panel on OTC miscellaneous internal drug products. The panel reviewed drug products for the relief of symptoms due to overindulgence in the combination of food and drink and hangover.

The panel concluded that overindulgence primarily presented various symptoms of an upset stomach. In contrast, the term "hangover" is used to describe symptoms experienced several hours after drinking large amounts of alcohol, and a review of the literature found over 30 different symptoms used to describe a hangover.

As no study identified the frequency of symptoms in a larger population, the panel created a list of the most frequently recurring symptoms found in the literature review and established the definition of a hangover as a condition consisting of a complex of symptoms involving the

gastrointestinal, neurologic, and metabolic systems that follows recent excessive alcohol ingestion. The symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.

The panel concluded that no clinical studies were needed to demonstrate efficacy, as it was logical to allow consumers to self-treat the wide variety of symptoms with analgesics, antacids, and stimulants, in this case caffeine, that were reviewed by other panels for treating these symptoms.

On December 24, 1991, the FDA published the tentative final monograph for overindulgence. The tentative final monograph added the indications of overindulgence in food and drink for antacids and for the antacid/analgesic combinations, and they added the indication of hangover relief for antacid/analgesic combinations for the GI symptoms, and analgesic/caffeine combinations for the fatigue or drowsiness symptoms.

The overindulgence monograph proposed rule also amended the antacid, internal analgesic, and stimulant monographs to add the related indications to these products. The tentative final monograph also ruled out antacid/analgesic/caffeine and antacid/caffeine combinations for hangover relief.

In considering the submitted comments and data related to all potential combinations of antacids, analgesics, and stimulants, the FDA concluded that given the effects of caffeine in stimulating gastric secretions and the target population of individuals who already have some degree of stomach or GI irritation or upset due to overindulgence in food or alcohol, the FDA concluded that it was irrational to combine antacids and caffeine since caffeine stimulates hydrochloric acid production and antacids treat symptoms associated with high levels of hydrochloric acid.

In summary, the overindulgence monograph added three new indications for the analgesic combinations, two for antacid/analgesic

combinations and one for analgesic/caffeine combinations.

The next three slides are a subsection of the summary chart in your background package. The first of the three overindulgence indications is for the temporary relief of minor aches and pains with upset stomach due to overindulgence in food and drink with associated symptoms of heartburn, fullness, and nausea, and the antacid/analgesic ingredients are antacid and acetaminophen in oral dosage form, and antacid and aspirin marketed in a form intended for ingestion as a solution.

The second of the three indications is for the temporary relief of minor aches and pains with upset stomach associated with hangover. The antacid/analgesic ingredients are identical to the previous indication.

The analgesic stimulant hangover indication is completely distinct. That indication is for the 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. The drugs for this combination is caffeine and acetaminophen or caffeine and aspirin in the oral dosage form.

The overindulgence monograph's amendments to other monograph regulations has the unintended consequence of creating a very complex monograph structure for the overindulgence and hangover indications with four affected monographs: the antacid, internal analgesic, overindulgence, and stimulant monographs.

Content relating to one monograph is only found in another. For example, as you can see in this slide, the definition of a hangover is found in the overindulgence monograph, the combination indication is found in the internal analgesic monograph, and the stimulant monograph cross-references the internal analgesic monograph for the indication.

As a result of all this rulemaking, there are currently three labeled indications for the antacid/analgesic combination products. The first

is the temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion, and upset stomach associated with these symptoms.

The second is the temporary relief of minor aches and pains with upset stomach associated with overindulgence in food and drink, with the associated symptoms of heartburn, nausea, fullness, belching, and gas. And the third is the temporary relief of minor aches and pains with upset stomach associated with a hangover.

Over the years, revisions to aspirin labeling has sought to improve the safe use of aspirin in individuals with stomach complaints. In addition to the previously mentioned 1988 aspirin warning, a new stomach bleeding warning was proposed as a tentative final monograph on December 26, 2006, which introduced a new stomach bleeding warning to mitigate risk with aspirin and other nonsteroidal anti-inflammatory drugs, or NSAIDs.

The TFM was proposed as a result of a September 20, 2002 NDAC meeting that reviewed data

regarding GI bleeding and made labeling change recommendations regarding a stomach bleeding warning for aspirin and other NSAIDs.

In 2009, the final rule established the stomach bleeding warning and other safety labeling changes for aspirin and other NSAIDs, and a stomach bleeding warning is published at 21 CFR 201.326. This regulation requires aspirin labeling to contain a stomach bleeding warning, which states, "This product contains an NSAID, which may cause severe bleeding. The chance is higher if you are age 60 or older; have had stomach ulcers or bleeding problems; take a blood-thinning anticoagulant or steroid drug; take other drugs containing prescription or non-prescription NSAIDs such as aspirin, ibuprofen, naproxen, or others; have three or more alcoholic drinks every day while using this product; or take more or for a longer time than directed."

In addition, the 2009 final rule revised the "Ask a doctor before use if" drug facts warning by adding a bullet that refers to the stomach bleeding

warning as it applies to the individual consumer. It also simplified the original stomach complaint bullet to read, "If you have a history of stomach problems such as heartburn."

As a result, labeling for aspirin instructs the consumer to ask a doctor before use if they had a history of heartburn, a symptom for which the consumer might take an antacid/aspirin combination product.

In summary, currently, the monograph regulations provide for OTC marketing of antacid/analgesic combination drug products for concurrent symptoms. Due to safety concerns, the antacid/aspirin combination drug products are limited to dosage forms for ingestion as a solution. However, the antacid/acetaminophen combination drug products have no such limitation.

The combination of antacid and aspirin for the use of relieving GI symptoms has been a point of comment regarding safety throughout the rulemaking process, and the Antacid Advisory Panel and the Internal Analgesics Advisory Panel reached

different conclusions regarding the safety and labeling of these products.

In 1988, the FDA addressed those differences and safety concerns expressed in public comments by limiting the antacid/aspirin dosage form to solution and deferred to labeling as the means to assure proper use of the drug.

Labeling revisions in the interim have sought to improve the safe use of aspirin in individuals with a history of stomach complaints. This meeting provides the opportunity to reconsider the issue with more recent data and 28 years of labeling experience and revision. Thank you.

Clarifying Questions

DR. ROUMIE: Now, we'll take any clarifying questions for Captain Vienna. Please remember to state your name for the record before you speak.

Are there any questions from the panel?

CAPT VIENNA: Thank you very much.

DR. ROUMIE: I'm so sorry. Dr. Farber?

DR. FARBER: Neil Farber, UC San Diego. I was wondering in the past, if the various panels

took into account other risks associated with specifically alcohol ingestion, including, for example, acute pancreatitis or acute hepatitis, when you were looking at the combination products?

CAPT VIENNA: The advisory panel didn't look in depth at those. The tentative final monograph has a lot of discussion about both the effects on the liver and the effects with bleeding on the combinations of antacid and analgesics, aspirin and acetaminophen.

There's a lot more detail about those concerns in the 2009 organ warning because that 2009 rule, in addition to the bleeding warning, also established the liver warning for acetaminophen.

DR. ROUMIE: Dr. Lipman?

DR. LIPMAN: Dr. Lipman from Washington. I'm not sure if this is the appropriate time to ask, but it struck me when I was reading through background material. In your slide number 11, which equates upset stomach with hyperacidity, do we really know that -- I would ask my fellow

gastroenterologists, we see a lot of functional dyspepsia that is probably not related to excessive acid.

So I think this concept of sour stomach is only due to hyperacidity, probably be should be at least questioned or dropped.

CAPT VIENNA: I can speak to the preamble of the rules and the thinking of the panel. They focused on these terms as terms used by the consumer to reflect an experience rather than a causality.

Sour stomach and upset stomach were introduced as consumer-friendly terms for an OTC active ingredient. There was not necessarily an extensive discussion by the advisory panels regarding the etiology, the connection to those terms.

DR. LIPMAN: Yes. I've got no problem with these as consumer terms. I do have a problem of us making the scientific leap that a sour stomach equals hyperacidity. That's all.

CAPT VIENNA: It's possible that Dr. Parikh

will discuss some of that later. Again, I can speak to the rationale found in the preamble.

DR. ROUMIE: Any other clarifying questions?

(No response.)

DR. ROUMIE: Okay.

CAPT VIENNA: Thank you very much.

DR. ROUMIE: Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that you may have with industry such as consulting fees, travel expenses, honoraria, and interests in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the

beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with industry presentations.

Industry Presentation - Barbara Kochanowski

DR. KOCHANOWSKI: Thank you. One change to the agenda you have in print, Dr. Damaris Rohsenow will be speaking before Brenna Haysom. So same speaker, slightly different order.

Good morning. Thank you for the opportunity to speak about the important issues of OTC analgesic-antacid combination products, as well as the clinical relevance of the hangover as an indication under the OTC monograph.

I'm Barbara Kochanowski, senior vice president of regulatory and scientific affairs for the Consumer Healthcare Products Association, or CHPA. I'm here today representing our members,

the manufacturers of over-the-counter medicines.

The CHPA has represented the self-medication industry for 136 years. Our mission is to empower self-care by preserving and expanding choice and availability of consumer healthcare products.

CHPA is serving as the overall industry sponsor for this meeting. Two of our members who manufacture products relevant to today's conversation will be speaking to you, Bayer Healthcare and Rally Labs.

We'll be providing information to help you as you deliberate on the questions FDA has asked. Specifically, Bayer will provide their perspective on the safety and effectiveness of the combination of aspirin and antacid based on more than 80 years of experience with the Alka-Seltzer brand.

The safety profile of this combination is very strong over many years and millions of uses. We're unaware of any acetaminophen-antacid combination product marketed for pain and upset stomach even though this combination is currently permitted under the OTC monograph.

Rally Labs will provide their perspective on a relatively new brand, Blowfish, a combination of aspirin and caffeine marketed for the relief of symptoms of hangover. This is also a permitted combination under the OTC monograph and specifically addresses two key symptoms typically associated with a hangover. It has a very favorable safety profile.

I'll now turn the podium over to the Bayer team, led by Dr. Andre Schmidt.

Industry Presentation - Andre Schmidt

DR. SCHMIDT: Good morning. My name is Andre Schmidt. I am the head of the U.S. medical affairs department for Bayer Consumer Health. I'd like to start by thanking Dr. Roumie, and the joint committees, and the FDA for giving us the opportunity today to participate and to provide our perspective on the topic of safety issues associated with OTC analgesics-antacid combination products.

Bayer is a leading innovator and provider of OTC medications. We are committed to the

development and marketing of products that make a difference in our consumers' lives. We diligently assess the safety of our products on an ongoing basis. The benefit-risk profile for Alka-Seltzer aspirin/antacid combination products is and remains favorable when used as labeled.

In recent years, we have focused our U.S. consumer innovation on Alka-Seltzer products for the relief of upset stomach and occasional heartburn. These new products have resonated extremely well with today's consumers.

Additionally, we acknowledge the ongoing discussions regarding this class of products. Given the shift in our strategy and to eliminate or reduce any potential for consumer misuse, Bayer has made the decision to reformulate all Alka-Seltzer aspirin/antacid combination products by removing the aspirin component and the analgesic indication.

I'd like to share some background on the Alka-Seltzer effervescent products. These products have been introduced to the U.S. market in 1930, and they have millions of use experience per year

worldwide.

Only a few Alka-Seltzer products contain the formulation that we are discussing today. These products are Alka-Seltzer Original, Alka-Seltzer Lemon Lime, and Alka-Seltzer Extra Strength. In the period from 2010 to 2016, an average of 1.4 billion doses of these products have been sold in the U.S. market.

These three Alka-Seltzer products all consist of a monograph-recognized antacid ingredient, citric acid, and sodium bicarbonate co-formulated with the monograph recognized analgesic; in the case of Alka-Seltzer, aspirin.

The main difference between the formulations is the amount of aspirin. Alka-Seltzer Original, Alka-Seltzer Lemon Lime contain 325 milligrams of aspirin per tablet. Alka-Seltzer Extra Strength contains 500 milligrams of aspirin per tablet.

Hence, the dosing directions are different: 2 tablets every 4 hours for Alka-Seltzer Original, Alka-Seltzer Lemon Lime; 2 tablets every 6 hours for Alka-Seltzer Extra Strength. It's important to

highlight that the maximum duration of use for these products is 10 days.

We've heard an excellent presentation earlier today by Captain Vienna, so I will not spend much time on monographs. But I would like to highlight that the monograph dictates the indications and warnings that are carried by our products.

The Alka-Seltzer aspirin and antacid products are used for the temporary relief of pain alone or the concurrent symptoms which require the relief provided by both types of active ingredients. You can read the exact indications of the products here on this slide, but I'd like to highlight that it's important to note that these products are not indicated for treatment of GI symptoms alone.

All products carry the 2009 implemented revised stomach bleeding warning. It's also presented in detail by Captain Vienna.

I'd like to spend the next few minutes to evaluate the efficacy and safety of each of the

single ingredients of the Alka-Seltzer combination products. These ingredients together are very efficacious and provide fast relief of the combined symptoms, pain such as headache, with accompanying GI symptoms.

The fixed-dose combination is convenient for consumers experiencing the combination of these symptoms and ensures appropriate dosing. This combination is proven by the millions of consumers using it every year.

The combination of sodium bicarbonate and citric acid is a monograph-recognized pH buffering agent. This combination is demonstrated to be highly efficacious in the treatment of symptoms caused by gastric acid by increasing the gastric and esophageal pH.

This study from 2002 shows a comparison of Alka-Seltzer effervescent to placebo. Subjects received a meal to provide high gastric acidity, and the intragastric pH was monitored over the study period of 5 and a half hours.

As you can see on this graph, the first

increase of gastric pH after intake of Alka-Seltzer is represented by the blue line as compared to placebo represented by the red line. This clearly demonstrates the high efficacy of the antacid components contained in the Alka-Seltzer combination products.

A few words on the history of aspirin. The active ingredient found in aspirin, salicylic acid, was used for thousands of years for the relief of pain and inflammation. The first clinical trial was published in Lancet in 1876.

In 1897, Felix Hoffman, an employee of Bayer, found that adding acetyl group reduces the irritant properties of salicylic acid. Two years later, in 1899, the modern aspirin was introduced to the market by Bayer.

In 1971, Sir John Vane described aspirin's mechanism of action. Since then, thousands of clinical studies on the use of aspirin in a wide variety of different indications, such as prevention of major severe cardiovascular events, have been published. And even today, aspirin

continues to be one of the most researched drugs in the world with an estimated 700 to 1000 publications every year.

The mechanism of action is well known and described. Today, we know that the cyclooxygenase pathway and the inhibition of COX-1 and COX-2 are mainly responsible not only for the analgesic anti-inflammatory and antiplatelet activities of aspirin but also for aspirin's effect on the gastric mucosa.

Efficacy of aspirin has been well established through thousands of clinical studies over the many years of its use. To demonstrate this efficacy, I highlighted two studies today.

On the left side, you see a study performed in non-migraine headache sufferers, performed at doses relevant for the OTC use from 250 milligrams up to 1000 milligrams. As you can see, all doses are significantly better than placebo at all time points. On the right side, you can see the recently updated Cochrane analysis from 2012, reconfirming the efficacy of aspirin in the relief

of moderate-to-severe post-surgical pain.

The safety profile of aspirin is well described and well characterized. Aspirin is generally well tolerated, and the adverse events are dependent on dose and treatment duration. When used short term and at OTC doses, aspirin has a similar safety profile as non-aspirin analgesics such as ibuprofen and acetaminophen. Serious adverse events are rare.

The gastrointestinal safety profile of aspirin is also extensively studied and well characterized. As mentioned earlier in my presentation, the effect on COX-1 inhibition on the gastric mucosa is known and well described. Additionally, there's also local effect as aspirin is a direct local irritant on the gastric mucosa. But the risk is also associated to underlying risk factors. A few of those were mentioned today when the stomach bleeding warning was presented.

The safety of short-term use of aspirin was extensively analyzed into recently published meta-analyses. The first analyzed

67 Bayer-sponsored clinical studies on aspirin on OTC relevant indications and dosing. For all of these studies, individual patient data is available.

The full range of OTC doses and duration up to 10 days were included in this meta-analysis. It's important to highlight that 82 of the patients included received a single dose of aspirin, which reflect the typical OTC aspirin use in the general population.

Major findings of this meta-analyses was increased dyspepsia with aspirin as compared to placebo. But important also for this meeting, GI bleedings were very rare, 1 bleeding in 6,181 patients randomized to aspirin and 3 bleedings in 3,515 patients randomized to placebo.

Also, important to highlight in this study, 2,298 patients on an effervescent aspirin formulation that is very similar to the Alka-Seltzer combination products were included. There were no bleedings in these patients treated with this product.

The second meta-analysis evaluated available literature on the short-term use of aspirin at OTC doses. You can see the same dose ranges and maximum treatment durations as seen in the meta-analysis before. However, a difference, 43 percent of the patients included in this meta-analysis received a single dose.

The results were very similar. In short-term use, aspirin was associated with a higher frequency of minor GI complaints. No GI bleeding was reported in any of the study arms.

The conclusions from the short-term aspirin meta-analysis, minor GI complaints such as dyspepsia are modestly increased with aspirin as compared to placebo. GI bleeding is very rare with short-term aspirin use.

I'd like to move now to our pharmacovigilance data. Bayer has robust processes and procedures in place to collect and evaluate postmarketing data and continually monitoring for any new safety information regarding the benefit-risk profile of all of our products.

Before we look at the reporting rates of adverse events, it's important to consider the fact that bleeding is a common clinical event, and it is associated with known risk factors such as age, concomitant medication, prior ulcer bleeding, and other risk factors.

Two recently published studies found a very similar incidence of upper GI bleeding leading to hospitalizations of around 60 per 100,000 per year. Dr. Loren Laine, one of the authors of this study, professor of gastroenterology at Yale University, is here with us today and available to answer your questions later today.

Also important, to understand the definition used to classify reported adverse events, an event is considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is considered medically significant or important.

At Bayer, we have a very conservative

approach by classifying a broad range of terms as automatically serious regardless of their clinical significance. In over 34 years of monitoring, we have received 5,042 reports, which is an average of 148 reports per year. Ninety percent of these reports were classified as non-serious. We received only 60 reports of GI bleeding, and of those, only 20 resulted in hospitalization.

When we take a closer look at the reporting rates, especially when we compare the rates before and after the implementation of the revised stomach bleeding warning, we see a very low and consistent reporting rate that can be estimated at 1 event per 2.4 million patients exposed.

This graphs shows you the numbers of serious GI bleeding reports from our spontaneous database. You see the dotted line marks the implementation of the stomach bleeding warning. We see very small numbers. We see no meaningful difference in the reporting rate of all these years and a consistently low reporting rate.

Consistent with what was presented by the

agency in their briefing material, we see that the majority of consumers reporting GI bleeding events also reported additional independent risk factors for GI bleeding. However, I'd like to highlight that this does not necessarily mean that these consumers inappropriately used these products.

To conclude our pharmacovigilance findings, the rate of spontaneous reports of serious adverse events with GI bleedings is low and has been consistent over time. Among the few consumers who reported a serious GI bleeding, many had labeled independent risk factors. Pharmacovigilance data support there is no change to the positive benefit-risk profile of these products.

You have seen this slide already. I'd like to highlight that we are committed to ensuring the safe use of all of our products. While we remain confident in the safety and efficacy of our products, I have also highlighted the reasons leading to the decision to reformulate.

We very much look forward to your discussion of this topic and appreciate the opportunity to

provide our perspective. Thank you very much.

Industry Presentation - Jay Sirois

DR. SIROIS: Good morning. My name is Jay Sirois. I'm the senior director of regulatory and scientific affairs at the Consumer Healthcare Products Association. I will provide some brief remarks regarding the topic of hangover as an indication within the FDA OTC monograph.

Although many definitions of hangover can be found depending on where you look and who you ask, all typically share several common descriptors. This one, which you've previously seen today, comes from a 1982 FDA notice of proposed rulemaking for OTC products indicated to treat overindulgence in alcohol and food.

It states that hangover is a condition consisting of symptoms involving the gastrointestinal, neurologic, and metabolic systems following a recent acute excessive alcohol ingestion. The symptoms can include nausea, heartburn, thirst, tremor, disturbance of equilibrium, fatigue, generalized aches and pains,

headache, dullness, and/or depression or irritability.

You have heard the excellent overview of the regulatory history of hangover under the OTC monograph provided by the agency. This indication was thoroughly studied by the expert panel and found to be amenable to treatment with a combination of OTC monograph ingredients under the internal analgesic, antacid, and stimulant monographs. CHPA believes hangover remains an appropriate indication for OTC medicines and supports the continued use of combination products for its treatment.

We have invited two renowned researchers with specific experience studying the clinical manifestations of hangover to speak with you today. They have a significant track record of NIH funding for this work and are founding members of the International Alcohol Hangover Research Group.

Dr. Damaris Rohsenow is a professor of behavioral and social sciences at Brown University and has published hundreds of articles and

chapters, primarily in the area of substance use and abuse, many specifically investigating the measurement of hangover symptoms. She was instrumental in developing an acute hangover scale for use in laboratory investigations.

Dr. Jonathan Howland is a professor of social and behavioral sciences and the director of the Public Health and Injury Prevention Research Center at Boston University. He has also published extensively in the field of hangover research and was involved in the development of the acute hangover scale.

Drs. Rohsenow and Howland are being paid by CHPA to be here as a resource to the committees and to provide perspective on FDA's questions about hangover.

OTC ingredients allowed under the monograph system for the treatment of individual symptoms of hangover include analgesics, antacids, and stimulants. Two brands of OTC products are shown here. Rally Labs markets an OTC analgesic stimulant product indicated for the treatment of

hangover.

Brenna Haysom of Rally Labs will provide more perspective on the hangover indication and the use of an aspirin/caffeine combination to treat symptoms associated with a hangover. First-aid shot therapy contains choline salicylate and caffeine. And as Dr. Kochanowski mentioned earlier, Dr. Rohsenow will present first, followed by Ms. Haysom. Thank you.

Industry Presentation - Damaris Rohsenow

DR. ROHSENOW: I was asked to start by giving a little bit of background to say why I consider myself an expert in alcohol administration research.

I started in the alcohol -- oh, I'm supposed to say I have no conflicts of interest, except I'm being paid by CHPA for my professional time and expenses in this presentation.

I started doing alcohol administration studies in the 1980s, bringing people up to 0.04 and 0.07 grams percent breath alcohol. I was a scientific advisor to the Vermont Alcohol Research

Center for their center grant, which brought people up to 0.05 and 0.10. That was when we established that nystagmus was the one sign that actually tracks breath alcohol unlike any other things in the field of sobriety test.

I conducted a study on medication effects on reactions to alcohol, and I'm currently a co-investigator on a contract from the National Institute on Alcoholism and Alcohol Abuse to test novel medications by administering alcohol.

In 1990s, I joined forces with Jonathan Howland who had expertise in occupational safety work. We started by doing low-dose alcohol administration work in ship simulator studies, finding significant impairment at 0.04 breath alcohol level on the ability to operate ship simulators safely. One of these was presented in a report to Congress by the director of the National Institute on Alcohol Abuse and Alcoholism.

We started doing hangover research in the 2000s in this foundation. We started by validating and publishing the acute hangover measure because

we needed to have a valid way to measure hangover.

We published papers on hangover resistance, several studies on the effects of drinking to 0.10, 0.11, or 0.12 grams percent on next-day ship simulator performance; on neurocognitive performance; on sleep architecture during the first and second half of the night to see if that mediated the effects on hangover or on neurocognitive performance the next day; the effects of beverage conjoiners on hangover and performance; next day academic performance; and mood on psychomotor vigilance.

We are two of the founding members of the International Alcohol Hangover Research group. As such, we co-authored the group's publication on the consensus statement about the best research practices for studying hangover and a separate article on that special issue in 2010 on the role of conjoiners and hangover.

The group has now published a consensus definition of hangover that appeared electronically online in January and is coming out in print in

current drug abuse reviews.

Jonathan Howland and I were invited to write a chapter on experimental methods for a textbook on injury research. We're known to be strong in methodology of hangover research. Since then, I've conducted secondary analyses of hangover from daily diary studies, et cetera.

I'll start by saying hangover is well known to everyone. It's well known to the general public. People usually think of it as the morning after the night before. When you see portrayals in the literature and movies, you mostly see pounding headache and feeling lousy as the primary things, symptoms that people are concerned about.

It's been studied in numerous surveys, many on college surveys and there are others. So it's well known to the public. There's no mystery there.

An interesting thing that Jonathan Howland and I discovered is that about 77 percent of people who drink enough really should be able to experience a hangover where most people experience

hangover do report getting hangover. When we looked across all surveys and all of our controlled studies, it means about 23 percent of people are actually hangover resistant, which was an interesting topic to study.

This is an overview, one I'm going to go through, and start with a definition because we need a definition before all else, a good solid definition: briefly, reasons to treat; briefly, methods to conduct controlled clinical investigations of hangover; the symptoms of hangover that we have found to be validated by controlled research; symptoms that are myths and that are still in the professional literature, including, I hate to say, some in the briefing book that came out that are not supported in controlled investigations; and the implications for medications.

In terms of the hangover, it's unpleasant symptoms, so it has to be unpleasant, and it's experienced after an episode of very heavy drinking. I'll get into how much heavy drinking.

It starts when blood alcohol concentration approaches zero.

The reason I'm more fussy about that rather than just saying just some time after heavy drinking is that it's easy to confuse intoxication effects with hangover effects. For example, people within a few hours after drinking heavily may vomit due to too much alcohol in their stomach, in their bloodstream, the toxic effects of alcohol ingestion itself. That's not hangover. So we look for when the blood alcohol level has fallen to closer to zero in order to be able to assert that it's hangover.

These are not intoxication effects. Some symptoms listed in the literature are actually intoxication effects. It's after most ethanol's worn off. It's not withdrawal. This causes confusion. Some of our colleagues have said it's a subclinical form of withdrawal. The withdrawal researchers I know say that that is not true. Withdrawal involves a pattern of chronically drinking to high levels and involves different

physiological systems.

There are other behavioral and cognitive effects. Jonathan Howland and I prefer the term "residual alcohol effects" to refer to all effects that happen after breath alcohol has fallen to near zero, but with hangovers, the subset that refers to the unpleasant symptoms.

We found that it requires a peak breath alcohol level of a least 0.11 to 0.12 grams percent. The way I discovered that was I went back to the laboratory studies that were done in 1970s where they actually had journal space enough to publish individual data on all of the participants.

Particularly Chapman in 1970 published individual data on all of the participants that were in his series of investigations where he used various doses of alcohol. He reported the actual breath alcohol level, peak breath alcohol level, people experienced and their actual symptoms that they experienced.

I took those data, and I charted it out so that I could have it by-breath alcohol level that

they obtained. And there seemed to be a breakpoint between 0.10 and 0.11 where you started having 55 percent or more people reporting moderate hangover once you got to 0.11 or higher grams percent.

So our first hangover study, we aimed for 0.10. Once I went back and did this re-analysis, we changed it to 0.11 to 0.12.

Some studies have had problems that it actually requires a breath alcohol near zero when you're assessing hangover in order to avoid a confound with alcohol intoxication effects.

There were some studies we found in the literature that assessed that when people were still at 0.04 breath alcohol, and then you have a confound; you don't know what you're getting. But at 0.02 and less, there tend to be no psychoactive effects of alcohol to speak of, so we count 0.02 the level that we aimed to get.

This shows the time course. Joris Verster in the Netherlands and I put together this chart for that consensus article on hangover methodology

in 2010.

This was dated from one of those studies in the 1970s, the Ylikahri et al. study in 1974, where they graphed the blood alcohol level. The numbers there on the left do not represent breath alcohol. It was a different unit. So if you can read those numbers, don't assume it tracks onto our grams percent.

You can see a time course of blood alcohol and the time course of reports of hangover severity. Hangover starts minimally when the blood alcohol has fallen to about half of its peak. As it goes down towards zero, then the hangover symptoms peak.

Breath alcohol reaches near zero about 10 to 14 hours after you finished drinking to a level that will bring you to 0.10 to 0.15 grams percent. That's the standard thing about 0.01 per hour that people lose after drinking on average. The hangover peaks at 10 to 16 hours after finishing drinking, but the peak lasts just a few hours, and so most of the hangover goes down rapidly within 2

to 3 hours of the peak.

Some reasons to treat hangover, there are safety reasons, economic reasons. In college, it can affect study. A study by Joris Verster said that 28 percent said they missed classes or work at school. Sixty percent said they often or were always unable to study while they're experiencing hangover.

In the workplace, 9 percent of U.S. employees have worked on hangover, and there's also absenteeism, often referred to as the Monday morning flu. And safety, we've got concern that safety-sensitive occupations might be affected by decreased accuracy when people need to act quickly.

We had found in our studies that people were about 2 percent slower in reaction time in a pair of our studies. Now, this may not seem like much, and when you're doing routine tasks, it may not affect your performance. But if you have to make fast accurate safety decisions, such as driving on the Beltway at 5 p.m., working air traffic control, working in factory settings where suddenly you need

fast, accurate decisions to prevent harm, then that slowed reaction could cause some safety issues.

Then there's just plain that people don't want to feel bad. There's just the plain relief of discomfort. The interesting thing is that many people get moralistic about hangover and say that if someone drinks that much, then they should be punished by feeling bad.

So part of it's that feeling that people deserve punishment. There's a second thing that some people raise. They feel that if someone is punished by having a hangover, then they are not going to become a problem drinker. But if that were the case, then no one would ever report more than one hangover.

Hangovers don't prevent people going on and to drink heavily in the future any more than how you feel after a day of skiing prevents you from going back to the ski slopes, or even a broken bone prevent you from going back to skiing the next year. So let people treat headache, and muscle ache, and nausea if they want to, is my attitude.

Controlled hangover investigation methods, I started on the basis of our standardly accepted methods for alcohol administration research, and we had to drive it up to a higher level. We wanted to avoid confounds with any other factors that could affect the hangover or performance under hangover, so we made sure we measured while people were not intoxicated.

We studied people the night after drinking to 0.10 to 0.12 grams percent. And on another night, they came in, and they had the same amount of a placebo beverage, and we studied them the morning after that so we could compare the mornings after the two nights. That's the only way to see what are valid symptoms and valid effects on performance.

We controlled for all nonspecific factors; we controlled for time in bed; we controlled for all nonspecific aspects of the drink, so everything except for the ethanol in the drinks. And as I said, our methods have become a standard in the field. We're recommended by the Alcohol Hangover

Research Group. We were the primary writers of the methods in that article.

We enroll heavy drinkers for safety, and they need to be people who drink at least as much as we're going to be giving them. We don't take a light drinker and give them this much alcohol. That would not be safe.

If you wanted to do studies just of hangover, you could just select people, the 77 percent who have had past hangover. We never did that. We wanted to look at the full range.

We use a clinical research unit that has beds that we could keep people in, controlled conditions, have a nurse or emergency medical technician on site to monitor people continuously by intercom and visual check every hour so they won't aspirate, vomit, and die.

We dose to the target peak breath alcohol. Instead of just using a grams-per-milligram dose, which we start with, gender-adjusted, because of individual differences in uptake of alcohol, if they don't reach close to the target breath alcohol

level within 15 minutes after they finish the drinking, then we give them a prorated, extra amount of alcohol so we can bring them up to the target breath alcohol level.

The nights when they get alcohol placebo drinks are counterbalanced. Half of the people get the alcohol drink on the first night; the other night get the placebo drink on the first night. So we can keep all the conditions the same.

We control the amount of opportunity to sleep. We obviously can't control the amount of time they're actually able to sleep, but we can at least enforce lights out so that there's nothing that they can do, except sit around in the dark or sleep during that time.

In the morning, we wake them up at 7:00 a.m. We first give them a breath alcohol test. We assess hangover if it's below 0.02, otherwise, we wait until the breath alcohol is down below 0.02 before we assess hangover and give any other performance measures.

These methods could be used for

investigating products. That's obviously not the focus of today's meeting, but it could be used to investigate products.

Now, before we could really study hangover, we had to figure out which symptoms of hangover appear to be valid and which weren't by going back to the previous data. The data from the 1970s, as I said, they reported actual hangover symptoms in some of the studies and report signs in some of the other studies.

There are three sources of materials I present, and I have a full citation list for these. Chapman, in particular, reported every symptom for every person.

There are a couple of studies that measure blood pressure, heart rate, tremor, paleness, perspiration, nystagmus. These were not supported. Blood pressure and heart rate did not track hangover severity. These other symptoms were not validated.

We looked at the symptoms that were reported across the subjects. Of course, you could have an

occasional symptom that one person reports, thinking it's due to hangover, but if other people aren't reporting it, it may not be.

We started with those in developing a measure. We took the 8 most common symptoms; plus we had people rate how hangover do you feel right now? We did not use the one symptom malaise because it's not used in the general public anymore. Going back, I wish I'd replaced it with the term "lousy," but it's not a specific symptom, so I think we're fine without that. We had people rate them from 1 to 7, from not experiencing at all to incapacitating.

Our measure was reliable whether we included that hangover rating in it or not. That was important because people were concerned that the hangover rating may involve a subjective attribution judgment, and so they wanted to make sure our measure is valid without it.

Then we validated each item by comparing it, the ratings, the morning after people had the high alcohol dose to the morning after they'd had the

same amount of placebo.

I put in yellow the ones that has statistically large effect sizes. All of the symptoms were significant. The ones with the largest effect sizes, the individual symptoms, are thirst, headache, and feeling dizzy or faint, and then the next highest is tiredness.

The tiredness and thirst are also elevated the morning after placebo, particularly tiredness. That's why the effect size for tiredness was not as large even though it was a very highly -- well, one of the highest rated symptoms in there. It's just there was less difference between alcohol and hangover nights. We all wake up tired and thirsty.

The heart racing, that's down there at the bottom. There was actually hardly any report of that. Since the measured heart rate was not affected, we can probably eliminate heart racing. So although it was significantly elevated, it's probably irrelevant.

Of course, we're going to the minimum level that we could safely bring people up of not getting

people really drunk as a skunk. These are mild-to-moderate ratings of hangover.

Then we did a re-analysis at someone's request of the percent of people who reported any rating of that symptoms as opposed to zero. We compared people who had said they'd moderate hangover to people who reported no hangover. The people with moderate hangover, 100 percent reported feeling thirsty and tired. Seventy-eight percent reported feeling headache.

The dizzy and faintness is probably highly correlated with being tired, and I think one of Verster's analyses showed that, so maybe secondary feeling tired. Then you get down to stomachache and nausea, and you're down to about 40 percent of people reporting that. So there's some distinction among the symptoms.

I put in yellow with the ones that were significant at the 1 out of 100 chance, and the other ones were significant at 1 out of 20 chance. If these numbers don't mean anything to you, that's okay. It indicates a degree of effect.

There are some other validated symptoms that we found. I was involved in a study where people kept daily diaries for 8 weeks, and they recorded their drinking every night. They reported on just 5 symptoms in the morning -- Kristina Jackson was the lead author on this -- and involved tired, headache, nausea, feeling weak, and difficulty concentrating.

Since we were able to determine which nights people drank to an estimated 0.11 grams percent or greater as opposed to nights when they drink less, we aimed to show that the ratings in all five of these symptoms were significantly higher on nights after they drink to 0.11 grams percent. So that adds very weak and difficulty concentrating as ones that have been validated under controlled circumstances.

Symptoms reported in the literature that are not hangover, as I said, some of my colleagues have thought that hangover might be a subclinical withdrawal. These withdrawal symptoms of tremor, increased heart rate, increased blood pressure,

they were not supported in those early studies in the 1970s, so they should probably be removed.

Intoxication effects, some people have, in their measures, trouble sleeping. The problem is trouble sleeping is something that occurs while alcohol is in the body. We did indeed find trouble sleeping, but that's while people are still intoxicated, so we can't claim that that's a hangover effect.

Memory loss or blackout, that occurs while people have a high breath alcohol level as well, so those should not be considered to be hangover symptoms.

What really annoys me is this word "diarrhea" that gets reported by some of my colleagues again and again. We've never saw diarrhea in any of the hundreds of people we ran through our studies. It wasn't reported in any of those 1970s studies.

I tried to figure out where it came from. One person developing their own measure in the early 1990s decided to put diarrhea as one item in

the measure. They didn't report that anyone reported diarrhea in that study. He reported that his overall total score was higher.

But that one item has been repeated by different authors in publications again, and again, and again. And I have this campaign to try to remove that and spread the information. Diarrhea we never saw, and the general public don't tend to talk about diarrhea, so I think we can forget that one.

There are emotional reaction to having drunk excessively such as guilt, suicidal, shame. Those are probably thoughts about the consequences of what they did or the consequences of what they didn't remember doing but not direct effects of alcohol. I'm not really addressing depression and anxiety. Those could be direct effects of alcohol wearing off, but we didn't study those.

There's inadequate evidence for the observable signs of paleness, tremor, perspiration, and nystagmus where one of these early investigators took the mean of zero to 2 ratings

and found it correlated with hangover but didn't give any information about which, if any of those signs, were valid, while the other found no effects on these same signs.

Nystagmus we know tracks breath alcohol level very closely, so that's probably an alcohol intoxication effect, not a hangover effect. They're irrelevant to this meeting anyway, but it's information.

The final group, the most commonly reported symptoms, all can be self-identified by people. People know if they have headaches, stomach distress. A cluster I think of as tired, dizzy, faint, weak, trouble concentrating; those probably go together, and thirst.

There may be some different underlying processes for each. There's some evidence for cytokines underlying the headache. The stomach distress may or may not be due to acid or other stomach irritation. The tiredness may be due to the sleep disruption. We certainly thought sleep disruption, particularly in the second half of the

night in our controlled studies, and thirst, of course, due to the diuretic effects of alcohol.

Those are the clusters, I think, as the most common. There are individual minor symptoms that other people report in surveys, but often they're reported by a fairly small proportion of individuals and surveys.

In this January 2017 article on consensus definition, Joris Verster also has a nice chart showing some intercorrelations of things, and they're off to the side and just correlated with these primary symptoms of hangover.

Implications. Drinkers can identify for themselves what these symptoms are that bother them and that they want to deal with. When I talk to MDs, the most consensus for treating symptoms, it does involve over-the-counter meds and water for the thirst. You're thirsty, you just drink. That's easy.

As we're talking about headache, a mild, preferably, anti-inflammatory pain killer. I like to think of any inflammatory because of the

cytokine release. As was brought up, you never let heavy drinkers use acetaminophen because of the serious liver toxicity.

Drowsiness, fatigue, caffeine, or they can take a nap, sleep somewhat. If they have to go to work, then they may want the caffeine. I find a good cup of coffee does me fine, but I've never experienced hangover myself. There's another disclosure.

(Laughter.)

DR. ROHSENOW: Not because I drink so much and don't have it and will resist. I just don't drink that much.

Of course, upset stomach, physicians I talk to refer to antacids.

I haven't heard of any products or prevention that I think can be recommended. Usually, they involve some combination of a sugar and a vitamin. Any treatment studies that were done are usually done oversees because there's no way the National Institute of Health will fund us to find a way to treat hangover.

Fructose, glucose, no effect. B vitamins, no effect. Multivitamins, no effect. Artichoke, don't ask me why that was in there, but they tested it. There's weak evidence of some herbal products, but basically, the commercial products I've seen, as far as I know, other than present company, the prevention products have no basis that I know of and I don't think have gone through INDs.

I just wanted to give an example of a bad basis I've seen. This just came out. Two Yale seniors have put a website up about a product called SunUp, vitamins and green tea extract.

I was contacted by Newsweek because they claim to have a scientific basis that addresses the root causes of hangover. They said one root cause is acetaldehyde. They cite a non-peer-reviewed conference presentation that doesn't mention hangover. And acetaldehyde, we know from Ylikahri 1974, is not correlated with hangover.

Vitamin loss. Vitamins don't affect hangover. Sure, give people vitamins, that's nice, but it doesn't affect hangover.

Glutamine rebound, I don't know of any evidence for that. They say that it results in increased blood pressure and tremors, but we know that's not hangover.

Cytokine production, sure, that's a good guess, but three of these four bases are not supported.

Conclusions. Hangovers are a definable medical condition. They can be induced under controlled conditions and eliminate confounds and alternative explanations. You can assess hangover symptoms by self-report, and we do have validated symptoms. Symptoms are then identified. They are greater after heavy drinking than after placebo, and that's valid. And as I said, the tiredness, thirst, stomachache, or nausea, and headache are the four clusters.

People may not get all these symptoms each time they have a hangover. Though everyone in our lab left tired and thirsty, 78 percent reported a hangover, so most people reported a hangover. Only about 40 percent reported nausea or stomachache.

Of course, this is at the starting level of dosing that would get people to hangover. So I went back to the one of the surveys where people can self-administer much higher levels of alcohol, and then you have about 81 percent of people reporting nausea.

The problem with surveys is they may be mixing intoxication period with hangover period, but this is what was found. Anyway, there may be individual differences in the symptoms.

Everyone wanted to become less tired, and those with worse hangover will want to treat headache and nausea as well. People know what feels bad, and there's no evidence for marketed prevention products, my final summary.

Industry Presentation - Brenna Haysom

MS. HAYSOM: Good morning. My name is Brenna Haysom. I'm the founder and CEO of Rally Labs, which makes Blowfish for hangovers. Thank you very much for the opportunity to speak to you about hangovers and their place within the OTC monograph this morning.

When I first started looking at the hangover category in 2006, I identified that there was an unmet consumer need. And I specifically chose to develop an OTC product rather than a dietary supplement because it was important that our product be safe, be very clear about what it did, and that it really work.

I'm very proud that Blowfish is an effective product, and we also really care about the safety of our consumers. So we welcome FDA's efforts to finalize the monograph, which we believe confirms the safety and effectiveness of the product.

Just a quick background on Blowfish, it's an aspirin/caffeine combination marketed under the analgesic and stimulant monographs for relief of hangover symptoms. Note, the product does not make antacid claims.

The product has been on the market since 2011. You may have noticed that the briefing materials don't reflect any sales of our product, which is incorrect. We've sold millions of doses since we introduced it, and we've not had a single

SAE. So the absence of FAERS reports, which is correct in the briefing materials, is actually meaningful data to support the safety of the product.

Hangovers are obviously a very common condition. Clearly not all, but most people in this room have probably suffered from one at one point or another. They're obviously also very unpleasant, and so a large number of consumers are actively looking to treat these symptoms.

Each month, there are an average of 90,000 Google searches that involve the word "hangover." This graph shows the average number of searches each month; it varies a little bit seasonally.

Hangover is the red line, and you can see that it peaks in January, which is due to New Year's Day. Just to put that 90,000 in context with other OTC indications, it compares with an average of 110,000 for heartburn and headache, so about 20 percent lower than that. But it is greater than cough and significantly greater than congestion and upset stomach.

Most of these 90,000 searches are around things like hangover remedy, how do I cure hangover, things like that. About 200 a month are hangover-cause, which shows that there are not very many people who don't understand why they're hung over.

What this clearly demonstrates is that people know what a hangover is, and they're searching for the best way to treat their symptoms in numbers that are comparable, and in some cases greater than many other indications in the monograph, so hangover clearly remains an appropriate indication to include in the monograph.

Just to speak a little bit about our consumers and their behavior, the average age is 28 years old, so this is a relatively young and health population. Eighty percent of our target consumers have had a hangover in the last month, so they're common, but they're actually not that frequent. Both our consumer research and our sales data shows that generally people have hangovers about twice a month. That number is slightly

higher for men, slightly lower for women. And the vast majority of these are described as either mild or moderate.

To talk a bit more about hangover symptoms, consumer research shows that the most common complaint is headache cited by 75 percent of people, followed closely by tiredness and thirst. So there's a clear logic to treat the condition with an aspirin/caffeine combination in a form that includes 16 ounces of water, an effervescent.

This is obviously consistent with the findings that Dr. Rohsenow just presented, and it's also notably consistent with the symptom complex used by the expert panel in making its recommendation and adopted by the agency in the tentative final monograph.

Just to talk a bit more about the expert panel's discussion of the term "hangover," they are explicit about the fact that a hangover refers to a condition several hours after ingestion of alcohol. This was just confirmed in Dr. Rohsenow's presentation that hangovers start when breath

alcohol levels approach zero and peak about 10 hours after drinking stops. So the point here is that this is long after ethanol has left the upper GI tract.

Second, the expert panel noted specifically that hangover, which is associated with sporadic ingestion, is differentiate from alcoholism. This is also consistent with our consumer research that shows that hangovers typically occur about twice a month.

I bring this up to show that the recommendation of the expert panel was based on assumptions that remain true today, both in terms of consumer understanding of the term and the current medical research about the condition.

I also want to make the point that the expert panel was clearly mindful of the health implications of heavy chronic alcohol consumption in making its recommendation and clearly differentiated that from hangovers as we showed in our discussion today.

Between 1975 and 1991, the expert panel and

FDA spent considerable time evaluating the evidence on hangovers and hangover drug products. They concluded that hangover was an appropriate indication for the monograph and that it was rational to treat hangover symptoms with combination products.

Since that time, all of the bases upon which they proposed the hangover indication remained valid. It's a commonly recognized symptom complex. There's a long history of consumers safely self-treating these symptoms with combination products, and clinical studies are unwarranted given the extensive review of the individual ingredients for these symptoms by other panels.

The agenda today includes evaluating safety of a number of combinations currently included in the monograph for hangover symptoms. As it relates to the specific ingredients, I am restricting my comments to aspirin/caffeine combinations, not acetaminophen or aspirin products that make an antacid claim.

There's no new evidence to support reversing

the carefully considered recommendation of the expert panel and FDA in the tentative final monograph. As noted by the expert panel at the time, there's a long history of use and extensive support for the safety of aspirin and caffeine for hangover symptoms.

We have had no SAEs, serious adverse events. There are no studies provided in the briefing materials that raise concerns that were not included in the discussion of the expert panel at the time or that raise any new concerns about these ingredients that are specific to hangovers.

As noted earlier, we're aware that since the publication of the tentative final monograph in 1991, FDA has evolved its position on the risk of NSAIDs and heavy chronic alcohol use. As noted by the expert panel and supported by our consumer data, this type of alcohol consumption is distinct from hangovers.

There's no data that indicates that an aspirin/caffeine combination for treatment of hangovers has a different profile than

aspirin/caffeine products marketed for headaches or for NSAID products generally.

We also note that, as demonstrated in Dr. Rohsenow's research, hangover symptoms generally subside within a few hours, so the hangover indication does not pose a risk associated with heavy long-term use of NSAIDs.

We've reviewed the literature referenced in the FDA briefing materials and found no evidence to discourage the use of the aspirin/caffeine combination for hangover symptoms. The study cited on the impact of alcohol in the GI tract relate to either damage caused by long-term alcohol abuse or immediately when ethanol is introduced into the GI tract. Neither of these applies to the hangover condition.

Further, these effects were known at the time of the expert panel's work and are mentioned in the discussions so were clearly considered in making their recommendation.

As it relates to caffeine in GI effects, the 1999 study cited in the briefing materials was

based on coffee, not caffeine, but found no association between coffee and dyspepsia. I'd just like to note that the evidence presented does not support the conclusion that caffeine is associated with dyspepsia.

The authors of that study further note that in some people, both caffeinated and decaffeinated coffee had similar GI effects, suggesting that coffee itself, not caffeine, is responsible.

A close examination of the literature cited by FDA in its discussion around caffeine and the stimulation of gastric acid in the 1991 tentative final monograph shows that none of the studies support concern under monograph conditions.

The evidence cited was based either on variable studies that use high doses of caffeine, outside the 100 to 200 milligram dosage of the monograph, or use coffee as a proxy for caffeine.

In a key 1975 study published in the New England Journal of Medicine, Cohen and Booth demonstrated that the effects of caffeine on acid secretion in lower esophageal sphincter pressure

were minimal in comparison to regular and decaffeinated coffee.

This would actually indicate that an aspirin/caffeine combination that used pharmaceutical caffeine would certainly be preferable to coffee that is self-administered in an arbitrary amount.

There's clearly a strong consumer demand to treat hangovers. It's just a fact that people are going to treat their hangover headache and fatigue. Without access to an effective OTC product that is clearly indicated for hangovers, it is likely that more consumers will use less safe alternatives.

There are over 200 dietary supplements that claim to prevent or cure hangovers. These products, which are obviously misbranded, pose particular danger because most were taken before drinking, which could lead consumers to think that they can drink without consequence. Even more concerning, some have names, like Sober, Sober Up, that could make consumers believe that the product will reverse intoxication.

On the other hand, they will self-medicate, typically with a pain reliever and some coffee, sometimes bacon, egg, and cheese, or Gatorade. We just covered the potentially negative effects of coffee on gastric acid, and if the panel determines that acetaminophen-based pain relievers are particularly dangerous after alcohol consumption, then it's even more important that pain relievers that are safe for hangovers, such as aspirin, be allowed to carry a specific hangover indication.

To conclude, our position is quite simple. Hangovers remain a widely recognized and clearly understood condition. There's a great consumer demand to treat these symptoms. Aspirin and caffeine have demonstrated safety and efficacy in treating these symptoms, and there's no data to suggest that taking this combination for a hangover is any different than the safety profile of the many aspirin/caffeine combinations marketed for headache.

We strongly agree with the findings of the expert panel and the FDA's position in the

tentative final monograph that consumers should continue to have access to the combination with a clear and specific indication for hangovers. Thank you.

Industry Presentation - Barbara Kochanowski

DR. KOCHANOWSKI: It feels like we've covered a wide range of topics. I just have two bullets to summarize.

In summary, aspirin and antacid combination products show a favorable safety profile over many years and millions of units sold. Hangover has a long history of being a consumer and professionally-recognized term for a collection of symptoms resulting from overindulgence in alcohol, and the associated symptoms can be safely treated with OTC products.

Currently marketed aspirin/caffeine products have a favorable safety profile. And CHPA believes there's no reason to avoid or discontinue use of this term or the OTC medicines to treat this condition.

We very much appreciate your attention.

Thank you for the opportunity to speak, and the entire group is open to take your questions.

Clarifying Questions

DR. ROUMIE: We'll now open for clarifying questions for industry. Please remember to state your name for the record before you speak, and if you can, please direct your question to a specific presenter. And I think I'll start with chair's prerogative. My question is for Dr. Schmidt.

In the briefing documents that we received, there was a reference to the pharmacovigilance meta-analysis data and individual level data that was presented.

My question is, does that pertain specifically to the products that we are reviewing today, combination products, or is that just your pharmacovigilance data on aspirin as a single and combo agent?

There were no confidence intervals around any of those estimates. I didn't know if you could provide any of those.

DR. SCHMIDT: Just to clarify your question,

you were talking about our pharmacovigilance data, not the two meta-analyses that were presented today.

DR. ROUMIE: That is correct. In the briefing document that you provided, I want to say it's page 11, but if you give me a chance, I'll tell you exactly.

DR. SCHMIDT: I would like to hand over the question to our pharmacovigilance expert, Dr. Barry.

MS. BARRY: Hi. Eileen Barry, Bayer, pharmacovigilance. Just to clarify, because I'm not sure I understand the question, is this regarding the Lanas meta-analysis?

DR. ROUMIE: It's the briefing document that was sent out. It's page 19, individual patient data-based analysis, bibliographic database analysis.

MS. BARRY: Okay.

DR. ROUMIE: Two issues, number one, there's no confidence intervals, so I'd like to see the significance of those results, those point

estimates. And then the second is, is this referring to combination products, or single agent, or both?

DR. SCHMIDT: Andre Schmidt, Bayer. I'm sorry I called the wrong expert here. You were referring to the Lanas meta-analysis, and I would like to ask Dr. Voelker to comment on your questions.

DR. VOELKER: Good morning. Michael Voelker, Bayer, global medical affairs.

Please, can you open up med [ph] 23A, slide 2, please?

The individual patient data meta-analysis, we did together with Professor Lanas from Spain, was a meta-analysis of Bayer-sponsored clinical trials available in the Bayer study repository in Germany.

From this study, we were able to analyze the individual patient data based on clinical study reports and based on case report form. In this analysis, we have seen no bleedings, 1 bleeding with aspirin, and 3 bleedings with placebo. The

aspirin formulation included in this analysis were all aspirin/containing products available within the Bayer study repository.

Now, we can talk about the Baron analysis. If we get up med 23B, please? Slide 2, please?

The Lanas meta-analysis investigated Bayer's cohort randomized-controlled trials. In addition to that, we did an analysis of the literature available, and this is a classic meta-analysis of the literature.

So we are summarizing what has been found in the literature regardless of the aspirin formulations. And due to the nature of the literature meta-analysis, we were not able to identify the products which are beyond the active ingredient. This is simply based on the active ingredient. Thank you very much.

DR. ROUMIE: Thank you. Dr. Farber?

DR. FARBER: This is also for Dr. Schmidt. I wonder if you have any available data on other NSAIDs to compare with aspirin data in terms of bleeding events to give us some sense of the

significance of the problem.

DR. SCHMIDT: I don't have comparative data of other NSAIDs here with me, but I might ask Dr. Laine maybe to comment on his experience in that area.

DR. LAINE: I'm Loren Laine, a gastroenterologist, professor of medicine at Yale. And as an aside, I was a member of the advisory committee in 2002 that Captain Vienna discussed that helped develop the stomach bleeding label. I'm also supposed to say that I'm being compensated by Bayer for my time here, but I have no financial stake in the outcome of the meeting.

Now, if I can remember your question, basically, in the short term, if you're looking just at over-the-counter, not great data, but similar studies show, surprisingly perhaps, that there's almost no bleeding episodes in short-term OTC NSAIDs given at doses and durations similar to aspirin.

Now, certainly, when you start taking the NSAIDs longer term, such as arthritis patients,

then the incidence of complications such as bleeding occurred about 1 to 1 and a half percent per year. For low-dose aspirin, long term, it's much lower, and then for high-dose aspirin, it would probably be similar to the traditional NSAIDs.

DR. ROUMIE: Dr. Stergachis?

DR. STERGACHIS: You said that right. Thank you very much. Andy Stergachis. A couple of questions for Dr. Rohsenow.

My first is one of the most common symptoms reported to hangover is thirsty. With respect to that, to what extent is dehydration a risk factor, which may increase the risk of adverse effects to, let's say, aspirin? That's my first question.

My second is one on your slide 20, you indicate implications for treatment, caffeine. Is that based on your expert opinion, or is there a higher level of evidence to support your comment?

DR. ROHSENOW: Damaris Rohsenow, Brown University. My professional time is being paid by CHPA, but I have no professional interest in the

outcome of this meeting.

The first one, thirst, our studies in the clinical research unit, there were people who reported feeling thirsty. We never saw anyone seemed to have signs of dehydration, except when we had one or two people actually vomit during the alcohol intoxication phase who needed to go down to the emergency room and have IV fluids.

But the thirst didn't seem to be reflecting clinical dehydration as near as we could tell in the morning. It was just people just report feeling thirsty but without showing any other signs.

The second, those implications for treatment I discussed, they're just my opinion based on talking to other physicians. That's not an evidence-base.

DR. ROUMIE: Dr. Solga?

DR. SOLGA: This question is also for Dr. Rohsenow. I don't understand the use of rational and irrational so far today. There is oodles of biological uncertainty, I think, going on

that lead to regulatory uncertainty, and then, of course, there's subject factors. I guess that's the challenge of over-the-counter medicines.

So far, Dr. Lipman has touched on briefly some biological uncertainty about gastric acid and symptoms that I agree with. The FDA, so far, has provided us with one example of what they consider to be an irrational combination of an antacid and caffeine.

You gave us a lecture about what's hangover and what's not a hangover that I found to be very useful. But when you talked about what's not a hangover, you mentioned emotional ability, some regrets, some poor sleeps, headache, some of it blurs with hangover, some of it doesn't.

When we're thinking about subject factors, whether it's a hangover or not a hangover, let's call it the post-binge drinking complex, are subjects capable of quality rational thought when they're looking at a package label under these circumstances regardless of whether or not we're talking about an actual hangover or something that

is part of a port-binge drinking complex, rational versus irrational behavior, hung over in the morning?

DR. ROHSENOW: Well, let's talk about rational versus irrational thinking while hung over in the morning. When people are at high blood alcohol level, high breath alcohol level, of course, you may say their ability to consent or make good judgments is impaired.

Generally, to expect that when breath alcohol level falls to near zero, people are expected to be able to have rational thinking. But our evidence is that we gave whole batteries of neurocognitive tests in -- it was in one or two of the studies -- a battery of neurocognitive tests, plus graduate record exams, plus we had people take a test on some content material they had learned the day before but before they started drinking. And actually, we found no evidence on any of these cognitive measures in the morning. It was just attention reaction time measure.

So there's no evidence that their thinking

would be irrational in the morning. They were able to do graduate record exams just fine the morning after drinking the alcohol, and all the other neurocognitive -- what was the name of a neurocognitive battery? Anyway, a standardized neurocognitive battery.

So there's no evidence that their judgment, their ability to make sound judgments would be impaired once the alcohol has worn off.

DR. ROUMIE: Dr. Engle?

DR. ENGLE: Jan Engle. This is for Dr. Schmidt. I had a question about slide 17 and 18, where you talked about the rate of GI bleeding that was reported. My question is, was that an objective measure or was that self-reported, or how did those studies show that there was GI bleeding?

DR. SCHMIDT: So the question is regarding the reported events in the meta-analysis that's presented. I will hand over the question to Dr. Voelker because I believe in the first study, it was recorded adverse events in our clinical studies. I have to give the second part of the

question of how were the bleeding events captured in the Baron meta-analysis to Dr. Voelker.

DR. VOELKER: Michael Voelker, Bayer, global medical affairs. Indeed, the Lanas studies, which were Bayer-sponsored studies that the bleedings were self-reported and physicians assist, reference the bibliographic analysis. Bleeding is reported in the papers, and of course, we do not know what's behind that. We just can summarize what we have seen in the papers. It's a classical literature analysis.

DR. ROUMIE: Dr. Sanders?

DR. SANDERS: It's a question for Dr. Rohsenow. First, I'm surprised at what you just reported from Dr. Solga's question on neurocognitive impairment given that 1 in 4 individuals has low health literacy begin with.

But I'm concerned about two other vulnerable groups, and I'm wondering if you're done any research. One is subjects who take neuroactive medications, particularly antidepressive medications and attention deficit disorder

medication, and also adolescents, which I haven't heard you speak about a lot but are also vulnerable.

Have you done any research on those vulnerable populations, and if so, how do they perform differently?

DR. ROHSENOW: Damaris Rohsenow, Brown University, paid by CHPA, no other financial conflicts to report.

We took healthy people. We didn't study people on antidepressant particularly.

Did we exclude for antidepressant use?

DR. HOWLAND: Yes, we did and we also recruited students [inaudible - off mic].

DR. ROHSENOW: Yes. We excluded for antidepressant use. We recruited either students or cadets at the maritime academies, or in one case, some professionals, sailors who were coming back for their recertification so we could study some age effects.

However, in recent years, my recent publication, we did secondary analyses of the data

that had been collected using daily diaries in people who had been taking naltrexone or topiramate versus placebo for a period of weeks. And we looked at the week before, placebo run-up before they started any of the medications, and one of the three studies involved teenagers.

What we did find with the teenagers -- I wasn't administering alcohol. This is what they were administering themselves, so we looked at their hangover reports, and we find that the teenagers -- I think it was if they were under 18, they reported more severe hangover at the same drinking level as the older people. That's all I can say about the teenagers.

DR. ROUMIE: Dr. Farber?

DR. FARBER: Neil Farber, UC San Diego. This is for Dr. Rohsenow again.

You were mentioning about the neurocognitive effects of alcohol and the ability to make decisions. I'm wondering about another dimension, and that is the emotional dimension and how that affected their decision-making.

I wonder if you had done, for example, a PHQ-9 before drinking and during the hangover period or some other measure of depression and anxiety and whether it affected their decision-making.

DR. ROHSENOW: Jonathan Howland remembers the mood data results. I'm going to have him come up and talk about that.

DR. HOWLAND: Jonathan Howland, Boston Medical Center. My time is being paid for by CHPA today, and I have no other conflicts I'm aware of.

In one of the studies that we did, when we discharged the subjects after they had done their performance test, we gave them the copy of the POMS, which is a measure of mood status, asked them to fill it out at 5 p.m. that afternoon and send it back to us. We did see a decreased mood status in the subjects who had received alcohol as opposed to placebo.

DR. ROUMIE: Dr. Pisarik?

DR. PISARIK: I have a question for Dr. Rohsenow and/or Ms. Haysom.

Ms. Haysom, in her slide, said that clinical studies aren't warranted given extensive review of individual ingredients. The charge to the committee is we're concerned about the adverse effects of these OTC medications, but there doesn't appear to be any studies that show that they even work other than due to placebo effect.

I guess my question is, shouldn't we have clinical studies showing that it works? Secondly, for Ms. Rohsenow, she's done an extensive amount of work obviously on drinking. Have you done any studies showing that any particular medication helps with hangovers in your subjects?

DR. ROHSENOW: Damaris Rohsenow, Brown University, paid by CHPA, no other financial interests. We did no studies to try to treat hangover.

DR. PISARIK: Okay.

MS. HAYSOM: Brenna Haysom, Rally Labs. Your question is whether or not there's any evidence for the effectiveness of aspirin and caffeine on hangover symptoms?

DR. PISARIK: Correct, as opposed to just placebo.

MS. HAYSOM: It was the position of the expert panel and FDA at the time that given that these ingredients had extensive history and extensive data to support the efficacy for these particular symptoms that studies were unwarranted, so we share that view.

DR. PISARIK: Okay. I guess my question is then, we're considering the side effects of the medications, but we have no clear evidence that they even work for hangover.

MS. HAYSOM: Sorry. I'm just unclear on which the -- when you cite that there's no evidence that they're effective relative to placebo --

DR. PISARIK: Placebo, yes. If you gave people with hangovers placebo, they will get as well as fast as taking the aspirin/caffeine medication, if there's no clear evidence of benefit.

MS. HAYSOM: Sorry. I don't think I'm following what study you're referencing.

DR. ROUMIE: I believe Dr. Pisarik is saying that Dr. Rohsenow's data showed that the symptoms of hangover are self-limited and resolve within 3 hours. So is there any evidence that the combination products to treat hangovers would shorten that duration, that self-limited duration?

MS. HAYSOM: Understood. I'm not aware of any specific data of that nature, no.

DR. PISARIK: Okay.

DR. ROUMIE: Thank you. Dr. Choudhry?

DR. CHOUDHRY: Actually, my question is very similar, and for Ms. Haysom. I think what the FDA panel said is that no studies were necessary because of the complex symptom nature rather than asserting that there was positive evidence of benefit or safety.

On your slide 8, for example, you say extensive support for safety and efficacy of these ingredients for hangover symptoms, and I was just wondering if you could actually clarify that comment.

MS. HAYSOM: Sure. They recognized a

hangover as a complex of symptoms, so the approach taken was treat those individual symptoms because there are a number of underlying processes by which hangovers make us feel bad.

The approach taken was to address those specific symptoms, and the rationale was that these ingredients have been proven efficacious and safe in treating those symptoms. There's an absence of data that there are any specific safety concerns for the hangover conditions with those ingredients.

DR. ROUMIE: Thank you. Dr. Lipman?

DR. LIPMAN: Dr. Lipman, from Washington. I've actually got two questions, one for Dr. Schmidt. Maybe you're not allowed to answer this. But I was struck in the pre-meeting materials on slide number 1 that Bayer is giving up the analgesic component of Alka-Seltzer.

Does that make this whole discussion moot? I mean, are there other combination products out there with antacid/aspirin? Can you say why you've given it up? Because it's not marketing well, or you're not allowed to say?

DR. SCHMIDT: We will remove the aspirin component from all of our aspirin-containing products that also contain an antacid. We, from Bayer Consumer Health, will have no products available that have this combined formulation after removing.

DR. LIPMAN: Are you allowed to tell us why?

DR. SCHMIDT: Yes. I apologize. I thought I made it clear in the beginning. It's actually two factors that come together.

The first is we innovated over the last couple of years and we brought new products to the market that are solely focused on the treatment of upset stomach and heartburn, occasional heartburn without pain indications.

These products, we see strong consumer purchase trends toward these new products over the last couple of years. Also, we acknowledge, and indeed today's meeting is evidence, ongoing discussions regarding this class of product. So we at Bayer decided to eliminate -- or try to reduce or eliminate any potential misuse that might be of

concern of the agency or this committee by removing the analgesic component.

So it's a shift in business strategy towards products focused on occasional heartburn and upset stomach together with acknowledging the ongoing discussions that we see regarding this type of product.

DR. LIPMAN: I'm not even sure who to ask from the Consumer Healthcare Products Association or the FDA, are those products still out there that had --

DR. ROUMIE: There are other products that were referenced in the briefing documents, and I think the bigger picture is the rational combination of these products in the monograph.

DR. LIPMAN: Okay. Second question, Ms. Haysom, or Dr. Haysom, I've never heard of Blowfish. I don't know what it -- what is the product labeling?

Does it define hangover, and how does the taker of Blowfish not -- how do you make sure that people who are chronic alcoholics who have symptoms

of alcohol withdrawal are not using Blowfish, which then may be toxic?

MS. HAYSOM: Brenna Haysom, Rally Labs. Here's our label. To the first part of your question, the indication is for the temporary -- it's consistent with what FDA showed early on -- for temporary relief of minor aches and pain associated with a hangover, helps restore mental alertness or wakefulness when experiencing fatigue, or drowsiness associated with a hangover, also for the temporary relief of headaches or body aches and pains alone.

As an aspirin product, it's labeled with the stomach bleeding warning that all aspirin products have, which has the warning may cause severe stomach bleeding -- this chance is higher if you, among other things, have three or more alcoholic drinks every day while using this product.

DR. LIPMAN: I guess one of my issues is I don't understand hangover, and I've certainly been educated about it today. Is the average consumer going to be able to differentiate hangover from

alcohol, or chronic alcoholism, or alcohol withdrawal?

I think this is something that perhaps the committee has to wrestle with because in all honesty, I don't think that -- if I'm experiencing hangover, which I don't think I have for a long time, this label is tough to read. So it's a question for either.

DR. ROUMIE: Thank you, Dr. Lipman. I think we'll debate that a little further and discuss as the meeting proceeds.

Dr. Neill?

DR. NEILL: I had a question for Dr. Schmidt to clarify. Could you please tell me, will Bayer market a product with aspirin under the brand Alka-Seltzer or any Alka-Seltzer-type product?

DR. SCHMIDT: We have a product line that is called Alka-Seltzer Plus, and these products are indicated for the treatment of cough and cold symptoms. Some of these products contain aspirin. They're not part of the reformulation effort, and I think also not part of today's discussion.

After the reformulation for the classic Alka-Seltzer products that are targeted for GI use, no products will contain the combination of aspirin with antacid anymore.

DR. NEILL: Sorry. I didn't identify myself. Richard Neill. So to clarify, after the reformulation, there will be Alka-Seltzer products with aspirin but no combination of aspirin and antacid marketed as Alka-Seltzer brand?

DR. SCHMIDT: That is correct.

DR. NEILL: Will there be any other brand that's combination aspirin and Alka-Seltzer?

DR. SCHMIDT: Aspirin with an antacid?

DR. NEILL: I'm sorry. With an antacid, yes.

DR. SCHMIDT: No.

DR. NEILL: Okay. Thank you.

Next question is for anyone from industry, and I'll direct it as well to FDA perhaps to address later. Any of you from industry familiar with actual self-selection studies performed for the indication of hangover for any product?

DR. KOCHANOWSKI: Barbara Kochanowski. No, we're not.

DR. NEILL: Thank you.

DR. ROUMIE: Dr. Besco?

DR. BESCO: Kelly Besco, OhioHealth. I wanted to build upon what Dr. Lipman was discussing earlier about the labeling of the Blowfish product, so I guess my question is for Ms. Haysom.

It looked like from the label that was displayed on the slide that the dosing information was 1 to 2 tabs every 6 hours, and each tablet contains 500 milligrams of aspirin. In effect, the patient could be taking upwards to 4000 milligrams of aspirin per day, which I believe is the maximum dosage of aspirin per day. I just wanted to confirm that with you.

MS. HAYSOM: That's correct. But as Dr. Rohsenow discussed earlier and was just pointed, usually, the symptoms resolve within several hours. At least, our experience is that generally, people take one dose, maybe two doses but no more than that.

DR. ROUMIE: Dr. Stergachis? Sorry.

DR. STERGACHIS: Andy Stergachis, University of Washington. We'll get it right by the end of the day, yes.

This is also for Ms. Haysom. Your second slide on millions of doses sold since 2011 with no SAEs, there's a little footnote at the bottom about an 800 number. Do you have information you can share with us about AEs, not just SAEs, adverse events that have a bearing on our understanding the safety?

MS. HAYSOM: I don't have that with me today, but can submit it to the docket.

DR. ROUMIE: Are there any other clarifying questions? Dr. Besco?

DR. BESCO: Just building upon that question as well -- Kelly Besco, OhioHealth -- the SAEs that you commented on, are those just directly reported to Rally, or does that include reports that are also have been submitted to the FDA?

MS. HAYSOM: It includes reports from Rally, but I think the FDA briefing material shows that

the FAERS system showed no reports as well.

DR. ROUMIE: We will now take a 15-minute break. Panel members, please remember that there will be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience . We will resume at 10:35.

(Whereupon, at 10:19 a.m., a recess was taken.)

DR. ROUMIE: We will now continue with the FDA presentations.

FDA Presentation - Ali Niak

DR. NIAK: Good morning, ladies and gentlemen. My name is Ali Niak, and I'm a medical officer in the Division of Pharmacovigilance, Office of Surveillance and Epidemiology. I will be presenting the postmarketing safety data from the Divisions of Drug Utilization, Pharmacovigilance, and Epidemiology.

Here is the outline of the slide presentation. I will initially discuss the findings from drug utilization, followed by postmarketing data, and conclude with the

epidemiology findings and a summary.

I will now transition to the information from drug utilization. Before I present the data from drug utilization, I would like to mention that the FDA has specified that any combination aspirin/antacid products approved for GI upsets/hangover should be marketed in solution.

In practice, this means that these combination products are effervescent. Effervescent refers to combinations that include sodium bicarbonate in combination with citric acid.

Drug use analyses have used the term "effervescent" for both aspirin and acetaminophen combinations. For the purposes of the review, literature searches were performed both with and without the term "effervescent."

To provide context for the adverse events, we examined OTC product sales from manufacturers to U.S. retail pharmacies using the IMS National Sales Perspective database. The following combination products were searched: combination effervescent aspirin/antacid, combination effervescent

acetaminophen/antacids, and combination analgesic/caffeine products.

National estimates of sales for combination effervescent aspirin/antacid products were available for analysis. However, sales of combination effervescent acetaminophen/antacid products returned no results.

In addition, sales of combination analgesic/caffeine products were not included in this presentation because the majority of these products are marketed for other indications unrelated to the monograph used for the topic of discussion.

This graph shows the nationally estimated number of packages sold for effervescent aspirin products from manufacturers to U.S. retail pharmacies annually. Our findings show that combination effervescent aspirin/antacid products are widely sold. Total sales captured in this database range from 8.4 to 8.8 million packages sold annually.

Here are some of the known limitations of

the OTC data available to the agency: lack of direct availability to consumer sales; IMS health estimates capturing approximately 50 percent of the total OTC market; OTC sales that do not include data from internet sales, convenience stores, specialty stores, or vending machines; and data being captured by active ingredient only. It is also of note that data on indication for use were not available.

Now, I will present you with a brief summary regarding FAERS and the postmarketing data. The FDA Adverse Event Reporting System, or FAERS, is a computer database of spontaneous reports for human drugs and biologics. Reporting by manufacturers for OTC products has become mandatory since 2006. However, reporting by healthcare professionals, patients, and the general public is voluntary.

Since 1969, there have been more than 13 million reports, and since 2016, there have been over 1.6 million new reports, which include both OTC and non-OTC products.

FAERS is a drug safety surveillance tool and

has many strengths. It includes all U.S. marketed products and may include foreign products. FAERS includes all uses, both approved indications and off-label uses. For example, if a drug was approved for only schizophrenia, we may receive adverse event reports for patients with bipolar disorder or depression as well.

FAERS includes broad patient populations, such as the elderly, children, pregnant women, and patients with comorbidities who are often excluded from clinical trials. FAERS is simple and a relatively inexpensive reporting system.

When is FAERS most useful? FAERS is ideal for events with small or rare background rates, such as acute liver failure, serious skin reactions such as Stevens-Johnson syndrome, or progressive multifocal leukoencephalopathy. It is useful for events that occur shortly after exposure.

What is the impact of FAERS? FAERS allows for detection of events not seen in clinical trials, identification of trends in reporting possible risk factors such as certain patient

populations, and other clinically significant safety concerns.

As with any database, there are limitations. FAERS also has several limitations that are noted here. The quality of report is variable. The information is limited in some reports.

The FDA requires four parameters to be present in the MedWatch form in order for a case report to be acceptable. The four parameters include the identity of the drug, the adverse event, the patient, and the reporter. Case reports are often lacking in key information when evaluating differences in drug formulation. For example, it would not be possible to assess an issue that is associated with an oral solution and compare it to the tablet form of the same medication.

Another limitation of FAERS is that underreporting exists. Not every adverse event is reported. Additionally, it is difficult in FAERS to attribute events with high background rates or long latency periods to the product.

Another limitation is that causal relationship between a product and an event is not required for reporting to the FDA. Furthermore, reporting biases exist.

Also, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population. The actual number of events in the population, the numerator, and the number of exposed patients in the population, the denominator, are not known.

FAERS is also not helpful with the event that involves the worsening of a preexisting disease. Comparison of drugs, including those in the same class, is difficult and often inappropriate in FAERS. The time on the market and the actual drug is usually different. This would be more appropriate for a clinical trial or a postmarketing observational study with a controlled setting.

Lastly, FAERS is less useful if the intended therapeutic disease is reflected in the adverse event. An example is the use of a psychiatric drug

for a psychiatric condition and the adverse event of suicide.

I will now transition into a discussion of our case series, but before that, I will discuss the primary objectives.

The primary objectives of the FAERS review were to identify major bleeding events associated with the aspirin or salicylate component of OTC analgesic combination products indicated for hangover or overindulgence, and to identify liver toxicity events associated with acetaminophen component of OTC analgesic combination products indicated for hangover or overindulgence.

We did not investigate liver injury associated with effervescent acetaminophen/antacid products further because there are currently no marketed effervescent acetaminophen/antacid products available in the U.S. market.

This slide shows the reporting trend for aspirin/antacid FAERS reports for all bleeding events. A FAERS search using productive active ingredient, product name in verbatim [ph] was

conducted for the timeframe through 7/30/2016 and included the standard MedDRA query "hemorrhage." The purpose of this search was to include all reports of major and non-major bleeding events.

It is of note that high level search of all aspirin-containing antacids and standard MedDRA query of "hemorrhage" generated 96 worldwide reports of major and non-major bleeding events received since 1970. The first event was noted in 1967. These reports have not been duplicated.

This slides shows a breakdown of the FAERS cases by preferred terms. As you can see, gastrointestinal hemorrhage predominates, followed in decreasing order by hematemesis, melena, hemorrhage, gastric hemorrhage, and hematochezia.

The FAERS database will search to identify serious adverse events related to major bleeding associated with effervescent aspirin/antacid and analgesic/caffeine combination products indicated for overindulgence/hangover. Cases were included if reporting of major bleeding events resulted in hospitalization or a blood transfusion, and if

events had a temporal association with OTC combination products with aspirin or salicylate marketed for overindulgence/hangover.

A case was excluded if the bleeding event did not result in hospitalization or blood transfusion, or if the case did not report a bleeding event. Additionally, a case was excluded if it contained insufficient information to determine the severity of the bleed or to determine a temporal association with the product. And lastly, the case was excluded if a product reportedly used in the narrative did not contain aspirin or salicylate.

The FAERS search did not identify cases where combination products contained analgesics/caffeine components for indication of hangover or overindulgence. With regard to major bleeding events involving effervescent aspirin/antacid products, 20 cases were identified between January 1, 1969 to July 31, 2016.

Several reasons can be attributed to the limited number of FAERS cases that were obtained in

the case series. There may have been possible miscoding of products. Additionally, underreporting of older drug products such as aspirin with widely known adverse events, such as gastrointestinal bleeding, may have occurred.

A third potential reason may have been the Weber effect, which denotes that adverse event reporting peaks at the end of the second year after a regulatory authority approves a drug. It should also be noted that no requirements for manufacturers to report serious adverse events associated with OTC drugs to the FDA existed until the recent amendment to the Federal Food, Drug, and Cosmetic Act in December 2006, which meant that reporting of serious adverse events prior to 2006 may have been minimal.

Lastly, the paucity of information in individual reports to adequately meet a case definition may also have affected the limited number of FAERS cases noted in our search.

This table represents trends in receipt year for the 20 cases of major bleeding in

association with effervescent aspirin/antacid combination products from 1970 to 2016.

The major characteristics of the major bleeding event cases with use of effervescent aspirin/antacid combination products are listed in this slide. The mean age was 61 with a median of 67, and the age range was between 24 to 91. The male to female ratio was 6 to 13, respectively, with 1 case not reporting the sex of the patient.

A majority of the cases were from the U.S., and most were reported by a healthcare professional. A majority of the patients were hospitalized, and there was 1 case of death, which shall be discussed later.

Most of the listed reasons for use of effervescent aspirin/antacid combination products were for GI issues. Colds, pain, and hay fever were other indications for usage. Just less than half of the cases did not list an indication for usage. In addition to the effervescent aspirin/antacid combination products, co-suspect medications in descending order included aspirin,

ibuprofen, naproxen, clopidogrel, indomethacin, prednisone, and warfarin.

Most of the major bleeding cases were considered upper GI bleeds. The upper GI bleeds included duodenal ulcer, hematemesis/melena, gastric ulcer, gastrointestinal hemorrhage, gastric polyps, Mallory-Weiss Syndrome/hematemesis, and hematemesis/duodenal ulcer.

The three lower GI bleeds included rectal hemorrhage. One report may have had multiple locations of GI bleed. Of the 20 cases, 9 required transfusion, but 6 did not require transfusion. And in 5 cases, there were no reports of any transfusions.

The one fatal bleeding event case from the FAERS search was a domestic case from 1970 of a 69-year-old female patient who developed massive GI bleed and was hospitalized. The patient had been using aspirin and an effervescent aspirin/antacid combination, both medications with unknown dose, frequency, duration of use, and indication.

Her initial hemoglobin was 8 with no units

or normal range reported, which decreased to 5.3. The patient received multiple blood transfusions, 14 units, and was treated with an ice water irrigation of her stomach. The patient died on the 5th day of her hospitalization. No cause of death was provided and no autopsy was performed. No medical history was provided.

The FAERS findings revealed that patients in 80 percent of the FAERS cases involving use of combination effervescent aspirin/antacid products had at least one risk factor for developing stomach bleed, which included age greater than 60 years, concomitant use of antithrombotics, NSAIDs, or prednisone, history of stomach ulcers, and history of alcohol abuse.

It is of note that 40 percent of the cases reported using combination effervescent aspirin/antacid products for GI issues such as heartburn, indigestion, or GI pain.

With regard to the population-based observational studies, there were no relevant studies of analgesic/antacid or analgesic/caffeine

combination products. There were 14 randomized, controlled clinical trials, RCTs, for aspirin/antacid, acetaminophen/antacid, or aspirin/caffeine combination products.

Important limitations in these randomized, controlled clinical trials included short-term follow-ups which would preclude long-term assessments.

It is of note that one crossover randomized, controlled clinical trial by Damman in 2004 compared aspirin/acetaminophen/caffeine and aspirin/antacid combination products. The study reported that gastric mucosal erosions and bleeding events were observed more often in healthy subjects taking aspirin/caffeine combination products than with aspirin/antacid combination products.

In summary, the data revealed that total sales of combination effervescent aspirin/antacid products captured in the IMS database ranged from 8.4 to 8.8 million packages sold annually from August 1, 2011 through July 31, 2016.

There were no sales of combination

effervescent acetaminophen/antacid products captured during the review period. There were 20 FAERS cases of major bleeding events and combination effervescent aspirin/antacid from January 1, 1969 through July 31, 2013.

We acknowledge that there are few FAERS cases documenting major bleeding over many years of marketing. However, given the known gastrointestinal toxicity of aspirin, the FAERS data should not be interpreted as a lack of risk for serious gastrointestinal bleeding.

With regards to the population-based published studies and randomized, controlled clinical trials, they were largely uninformative, but one randomized, controlled clinical trial suggested gastric risks from aspirin/caffeine combination products. Studies will be discussed further in the next slide presentation by my colleague, Dr. Ketan Parikh.

In conclusion, I would like to thank all my colleagues for the input regarding this presentation.

FDA Presentation - Ketan Parikh

DR. PARIKH: Good morning, committee chair, members of the committees, ladies, and gentlemen. I'm Ketan Parikh. I'm a medical officer in the Division of Nonprescription Drug Products. An extensive literature review was done for the topics under discussion, and I will present some highlights of that review.

The literature search was performed using PubMed, EMBASE, and Google and produced over 250 articles. Articles that provided clinical safety information were included in the review.

The focus was on combination products intended to treat gastrointestinal and hangover symptoms, and not on single active ingredient products. Single active ingredient products are not the topic of discussion for this advisory committee meeting. Although the number of articles identified was large, the actual amount of data was somewhat sparse.

The literature search was primarily aimed at addressing two main clinical concerns that are

relevant for today's discussion. First, are the combination products containing aspirin for the treatment of gastrointestinal symptoms a rational combination, and do they have a negative impact on the GI tract? Second, does the use of acetaminophen-containing combination products for the treatment of a hangover increase the risk of hepatotoxicity?

Considering that consumers who have a hangover recently ingested alcohol and considering the effect of both alcohol and acetaminophen on the liver, are combination products containing acetaminophen a rational combination for the treatment of hangover?

Moving on to that first concern, do aspirin-containing combination products used for the treatment of gastrointestinal symptoms have a negative impact on the GI tract?

Before discussing aspirin/antacid combination products, here is some basic information about aspirin. Over-the-counter, or OTC, aspirin is indicated for temporary relief of

headache, minor aches and pains, menstrual pain, and toothache, and for reduction of fever from colds and flu.

The OTC dose of aspirin is 325 milligrams to 4000 milligrams per day. Aspirin is a nonselective cyclooxygenase inhibitor, and via this activity, it reduces prostaglandin and thromboxane synthesis. Aspirin's analgesic and antipyretic effects occur through dose-dependent reduction in prostaglandin E2 synthesis. Decreased prostaglandin synthesis also reduces multiple gastric mucosal protective mechanisms.

Aspirin decreases platelet aggregation through irreversible inhibition of thromboxane A2 production. Adverse events associated with the use of aspirin that are relevant to our discussion include abdominal pain, nausea, vomiting, heartburn, gastritis, and GI bleeding. Upper GI bleeding is the most frequent bleeding complication.

To address the risk of aspirin-related GI bleeding, a stomach bleeding warning was added to

the Drug Facts Label in 2009. Between 1998 and 2001, the FDA's adverse event reporting database received spontaneous reports of GI bleeding in individuals who used OTC nonsteroidal anti-inflammatory agents, or NSAIDs, including aspirin, as an analgesic and/or antipyretic.

Due to these case reports, the Nonprescription Drugs Advisory Committee, or NDAC, met in September 2002 to discuss a possible stomach bleeding warning and unanimously agreed that there was evidence of bleeding risk associated with OTC NSAIDs, including aspirin, and supported the stomach bleeding warning on the Drug Fact Label, or DFL, of all NSAIDs, including aspirin.

A proposed rule was published in the Federal Register in December 2006. After reviewing all of the comments and data, the final rule with organ-specific warnings was published in the Federal Register in 2009 and required stomach bleeding warnings on the Drug Facts label of all NSAIDs, including aspirin.

As presented earlier by Captain Vienna, the

stomach bleeding warning states the following: This product contains an NSAID, which may cause severe bleeding. The chance is higher if you are age 60 or older, have had stomach ulcers or bleeding problems; take a blood thinning anticoagulant or a steroid drug; take other drugs containing prescription or nonprescription NSAIDs; have 3 or more alcoholic drinks every day while using this product; and lastly, take more or for a longer time than directed.

Additionally, the "Ask a doctor before use if" warning was revised to include, stomach bleeding warnings applies to you or if you have a history of stomach problems, such as heartburn.

Despite these warnings, FDA continues to receive case reports of GI bleedings associated with the use of aspirin/antacid combination drug products.

Do aspirin-containing combination products have a safer GI profile compared to aspirin alone? There are some publications that address this. In 1973, The Medical Letter raised concerns regarding

claims that unlike plain aspirin, the aspirin/sodium bicarbonate/citric acid combination product did not cause gastric irritation. The article expressed a concern about using an aspirin/antacid combination product to treat GI symptoms since aspirin may cause gastritis and aggravate peptic ulcers.

In addition, the article reported that aspirin/antacid combination products have been associated with hematemesis and melena when administered after heavy alcohol intake.

An article reported that aspirin/antacid combination products may cause bleeding if used for dyspepsia. In 1980, the authors of this article reported a series of 10 patients who were admitted to a hospital in the United Kingdom after taking aspirin/antacid products for dyspepsia. Seven out of 10 patients required blood transfusions, 2 out of 10 required emergent surgery, and the majority of the bleeding was due to erosions or ulcers.

Many countries have withdrawn GI indications for combination aspirin/antacid products. In 2004,

Spain withdrew the aspirin component from the combination product and allows only the antacid component in the market for GI indications.

In 2005 and 2010, respectively, France and the United Kingdom removed gastric indications. An article from 2009 reported that 32 out of 68 countries, where aspirin/antacid combination products are allowed to be marketed, do not allow GI indications for this combination product.

We have just discussed aspirin/antacid combination products for GI indications. Another consideration is aspirin-containing combination products for hangover. Hangover is associated with multiple GI symptoms. Some combination products for hangover include aspirin.

Similar to the concern for aspirin/antacid combination products for GI uses, there is concern for potential adverse GI effects of aspirin-containing combination products, for example, aspirin/caffeine combinations for hangover.

A few points about OTC aspirin/antacid

combination products for GI indications, the relationship between aspirin/antacid combination products and GI bleeding remains a persistent concern, although data are sparse. In 2002, NDAC voted unanimously to add stomach bleeding warnings on the Drug Facts label of all NSAIDs, including aspirin.

The final rule was published in the Federal Register in 2009, requiring stomach bleeding warnings on the DFLs of all NSAIDs, including aspirin. Despite these stomach bleeding warnings, FDA continues to receive case reports of major GI bleeding events.

Moving on to a second concern, does the use of acetaminophen-containing combination products for the treatment of hangover increase the risk of hepatotoxicity considering that consumers who have a hangover recently ingested alcohol and considering the effect of both alcohol and acetaminophen on the liver?

Before discussing combination acetaminophen products for the treatment of hangover, here are a

few points about the effects of alcohol. According to the National Institute on Alcohol Abuse and Alcoholism, a standard drink in the United States is 14 grams of pure alcohol, which is found in 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.

Binge drinking is defined as a pattern of alcohol drinking that leads to blood alcohol concentration of 0.08 grams per deciliter or above. For males, that would require 5 drinks or more within 2 hours, and for females, 4 or more. Virtually, all chronic alcohol users will develop a fatty liver, but only a minority progressed to further stages of alcoholic liver disease.

Two most important risk factors are the amount and duration of alcohol use. Once alcohol is ingested, its primary metabolism occurs in the liver through oxidative and nonoxidative pathways. Alcohol and its metabolites primarily affect the liver but also may cause esophageal and gastric inflammation. Alcohol is a leading cause of acute liver failure.

A few basics regarding acetaminophen, it is indicated for the temporary relief of minor aches and pains, such as headache, muscle aches, backache, arthritis, the common cold, menstrual cramps, and toothache, and to reduce fever. The current OTC dose ranges from 325 to 4000 milligrams per day.

Adverse events associated with the use of acetaminophen that are relevant to our discussion include nausea and vomiting. A severe but less common adverse event is hepatotoxicity. Under normal circumstances, acetaminophen is metabolized through multiple pathways, but one pathway leads to formation of a liver-toxic substance called N-acetyl-p-benzoquinoneimine or NAPQI.

Due to the symptoms of a hangover which may include nausea and vomiting, consumers may significantly reduce their intake of nutrition and fluids, which may result in reduced glutathione stores in the liver and possibly increasing the risk of hepatotoxicity.

NAPQI rapidly conjugates with hepatic

glutathione, forming nontoxic cysteine and mercaptate compounds that are excreted in the urine. When hepatic glutathione stores are depleted or significantly reduced, NAPQI begins to react with hepatic cellular proteins and injury ensues.

Acetaminophen is the leading cause of drug-induced liver failure. About 50 percent of liver failure cases may be associated with acetaminophen overdose, and of these cases, half to two-thirds of acetaminophen overdoses are unintentional. Consumers often fail to recognize the consequences of exceeding maximum daily recommended dose of acetaminophen.

Does acetaminophen, at therapeutic doses, have a subclinical effect on the liver? One study addressed this question. This was a single-blind with only subjects blinded, placebo-controlled, five-treatment, longitudinal study on 145 healthy adults in two in-patient pharmacology research facilities.

The study subjects were administered either

placebo, 4 grams of acetaminophen daily, or 1 of 3 acetaminophen/opioid combination products that each contained 4 grams per day of acetaminophen.

All treatments were administered for 2 weeks. A mean of 39 percent of subjects in the acetaminophen arms had an alanine aminotransferase, or ALT, greater than 3 times the upper limits of normal. Twenty-three percent of acetaminophen-treated subjects had an ALT greater than 5 times the upper limits of normal.

The percentages of subjects with ALT greater than 3 times upper limits of normal or greater than 5 times upper limits of normal was similar across the acetaminophen groups. No subjects had a trough acetaminophen level above the therapeutic range. No placebo subjects had an ALT greater than 3 times the upper limits of normal. No clinical symptoms were reported by any of the study subjects.

You have just heard some information on alcohol and acetaminophen individually. Now, we'll go on to this question of whether acetaminophen in combination with a recent alcohol use increases the

risk of hepatotoxicity compared to use of either agent alone.

A review article published in 2000 that regular moderate to heavy alcohol use may potentiate the toxic effects of acetaminophen and found case reports of acute liver failure in moderate alcohol users who ingested as little as 4 grams of acetaminophen in 24 hours.

Alcohol may be a cofactor in lower-dose users of acetaminophen who develop acute liver failure. A study analyzed prospective data recorded on 662 acute liver failure cases that were admitted to 22 tertiary care hospitals in the United States. For 302 cases, medical records reported acetaminophen-related hepatotoxicity. The authors reviewed all cases and eliminated some due to a lack of data or competing etiologies, leaving 275 cases in the final acetaminophen acute liver failure study group.

Nineteen cases out of 275 cases of acute liver failure associated with acetaminophen occurred with less than 4 grams per day of

acetaminophen. Sixty-five percent of these cases met criteria for alcohol abuse, which was greater than 40 grams per day in men and greater than 20 grams per day in women.

This contrasts with a group that took more than 4 grams per day of acetaminophen. Only 37 percent of these met criteria for alcohol abuse. Overall, 22 percent of all patients used 2 or more preparations of acetaminophen.

The authors concluded that alcohol may be a cofactor in the acute liver failure cases that present after taking therapeutic doses of acetaminophen.

A study looked at the effect of acetaminophen on hepatic tests of alcohol detoxification patients from a prospective randomized, double-blind, placebo-controlled trial involving 443 adult alcoholic patients who were admitted to two medical centers for alcohol detoxification.

After excluding patients who had aspartate transaminase or alanine transaminase levels greater

than 200 international units, patients were randomized to acetaminophen, 4 grams per day, or placebo for three consecutive days. A total of 308 patients received acetaminophen, and 135 patients received placebo for three days.

Mean baseline ALT was no different between the acetaminophen and placebo groups, and mean peak ALT also did not differ between the acetaminophen and placebo groups.

In post hoc analysis, a total of 32 patients, 24 patients or 8 percent of the acetaminophen group and 8 patients or 6 percent of the placebo group, developed an ALT level greater than 3 times the upper limits of normal. A total of 11 patients, 9 or 3 percent in acetaminophen and 2 patients or 1 percent in the placebo group, developed an ALT level greater than 200 international units per liter sometime during the study. These post hoc analyses had limited power.

Although the main focus of this meeting is to discuss antacid/aspirin combination products for GI uses and acetaminophen-containing combination

products for hangover, there is an additional question.

Are analgesic/caffeine combination products a rational combination for the treatment of hangover symptoms? There are combination analgesic/caffeine products marketed for the relief of hangover symptoms.

Caffeine stimulates gastric acid secretion and reduces competence of the lower esophageal sphincter as reported by Cohen and Booth. Caffeine may exacerbate GI symptoms of hangover and may potentiate adverse GI effects of aspirin and of alcohol.

In summary, the relationship between aspirin/antacid combination products and GI bleeding remains a persistent concern at FDA although data are sparse.

The FDA continues to receive case reports of major GI bleeding events associated with the use of aspirin/antacid combination products. The bleeding appears to be associated with the aspirin component. It is unclear if aspirin/antacid

combination products are rational for combination for treatment of GI symptoms.

It is unclear if combination products containing acetaminophen are rational combinations for treatment of hangover. Acetaminophen is a leading cause of drug-induced liver failure in the United States. Moderate alcohol consumption may be associated with a higher risk of acetaminophen-related adverse events.

Consumers who use acetaminophen-containing combination products, particularly in the setting of recent excessive alcohol intake, may increase their risk of liver injury.

Caffeine stimulates gastric acid secretion and reduces the competence of lower esophageal sphincter. Consumers who use caffeine/aspirin combination products, particularly in the setting of recent excessive alcohol intake, may increase the incidents of gastric adverse events considering that alcohol, in itself, can cause inflammation of the esophageal and gastric mucosa.

Thank you for attention, and we look forward

to the committee's discussions. My fellow FDA presenters will now join me at the podium to answer any clarifying questions from the committee.

Clarifying Questions

DR. ROUMIE: Are there any clarifying questions to the FDA? Please remember to state your name for the record before you speak. If you can, please direct your questions to a specific presenter. We'll start with Dr. Farber.

DR. FARBER: Neil Farber, UC San Diego. For Dr. Parikh, you mentioned that the combination of analgesic/caffeine products in the setting of alcohol may exacerbate GI symptoms. Do you have any data regarding that issue?

We know that there's a logical physiologic presumption that may have occurred, but do you have any data that it does occur?

DR. PARIKH: As far as I could find, there were no clinically reported data that supports that, yes.

DR. ROUMIE: Dr. Stergachis?

DR. STERGACHIS: Andy Stergachis, University

of Washington. For Dr. Niak, two or three questions. One is, to what extent has the setting of care for GI bleeds had any effect on the data completeness? In other words, the data you shared with us are GI bleeds leading to hospitalizations or blood transfusions, but it's unclear to me whether serious GI bleeds are hospitalized these days. And you showed some data that not all blood transfusions -- not every case has a blood transfusion.

That's question 1. I'll just get my questions out real quick.

Second, do you have any data with respect to the occurrence of bronchospasm for asthmatics related to aspirin use? Because it might have some bearing on labeling.

Thirdly, you mentioned global regulatory action as it relates to the combination products, but I don't recall seeing anything in your slide about global regulatory action in relation to products for hangover. Thank you.

DR. NIAK: Thank you. With regard to the

first question, with regard to GI management of bleeds in the hospital, our FAERS search involved basically queries regarding hospitalization due to GI bleeding and/or transfusion and the time segment shortly after taking the medications.

In terms of other issues like serious GI issues, our premise, our approach was basically any patient that needed hospitalization secondary to GI bleeding, becoming symptomatic, hypotension, and whatnot, would basically be transferred to the hospital or referred to the hospital, and that was a serious issue.

In terms of bleeds such as like epistaxis, nose bleeds, and other issues where they didn't end up in the hospital, that certainly was not picked up. Certainly, even the epistaxis that continued and did not stop, we looked at that, too. So I hope I've answer your question, the first question.

With regard to the bronchospasm, we didn't look at bronchospasm with aspirin.

I'm sorry, your third question?

DR. STERGACHIS: Thank you. Global

regulatory action, if any, in the area of hangover.

DR. NIAK: I don't have any information regarding that, but I defer to my colleagues who might be able to have any input regarding that.

DR. ROUMIE: Thank you. Dr. Lipman?

DR. LIPMAN: Dr. Lipman, from Washington. I have two questions and a comment. The first question is for Dr. Niak; second one's for Dr. Parikh.

I'm confused about your data, FAERS reporting data. Slide 13 says 96 cases since 1969 or 1970s. Then the rest of your data is 20 cases, and then you emphasized the 20 cases. What is the difference between those two slides, and which of the numbers are we supposed to use? That's the first question.

DR. NIAK: Okay. The 96 cases, these were the standard metric query hemorrhage, which we had 96 cases. These were worldwide reports of major and non-major bleeding events. The 20 were basically major bleedings, ending up in the hospital and/or needing transfusions.

DR. LIPMAN: Then second question, if you've only got 20 reported events, and you're saying the reporting is sparse, and yet there are three slides in Dr. Parikh's presentation which said that the FDA continues to receive reports of adverse events related to bleeding, either you're receiving them and there should be bigger numbers or you're not receiving them. But in the three summary slides, you said that the FDA was continuing to receive reports.

DR. NIAK: Yes. Let me clarify. The MedWatch form which we use for FAERS basically has four parameters that needs to be included in order to be considered as reports. You need to have the identity of the drug, you need to have the patient, the reporter, and the adverse event.

We do get reports, but unfortunately, a lot of these reports, there's a lot of missing information, so therefore they're not counted as the information that we have. And therefore, that would be the reason for not having more numbers of complete reports.

Also, my colleague, Dr. McCulley, would like to add to that, please.

DR. McCULLEY: Hi. I just wanted to clarify that the additional reports that we received after the organ-specific labeling change in 2009, that FDA has received additional 8 reports of those major bleeding cases.

DR. ROUMIE: Dr. Schmid first.

DR. SCHMID: Chris Schmid, from Brown. I had four questions, but I'll ask the question and then ask you to respond, because otherwise, we're going to get --

DR. NIAK: Thank you.

DR. SCHMID: I think these are fairly quick. Do you have any information on the sales of analgesic/caffeine combination products?

DR. NIAK: I would like to defer this question to my colleagues in drug utilization, please?

DR. GREENE: This is Patty Greene. I'm a drug utilization analyst in DEPI II. We basically looked at combination analgesic/caffeine products,

and we could only search by active ingredient. But what we found was that we were capturing more products that were relating to menstrual pain and headache, and they were not appropriate for this setting. So we actually did not have a good capture of that particular class of products.

DR. SCHMID: Okay. Thanks. You talked about acetaminophen and its risk with hepatotoxicity. Are there any products actually marketed with combination of acetaminophen and caffeine?

DR. GREENE: I'm sorry. Could you repeat your question?

DR. SCHMID: Are there any combination products with acetaminophen and caffeine? I know there are with aspirin and caffeine?

DR. GREENE: Yes, there are acetaminophen products.

DR. SCHMID: Okay. Third question is you'd mentioned that the FAERS database, one of the limitations is underreporting, but you said you didn't have specific numbers in this case. Do you

have numbers overall as to how susceptible FAERS is to underreporting in any circumstances?

DR. NIAK: Basically, I'll go back to the -- in 2016, there have been 1.6 million new reports basically, and of these new reports, this includes both OTC and non-OTC.

Of these 1.6 million, there's between 10 to 20 percent that are OTC products. The problem is that there's a lot of overlap. There are patients who might use the prescription medications and cut them in half and use them as OTC, and that kind of adds a little confusion. And there are patients who might use the OTC dosages in the prescription dosages.

So in terms of the actual numbers, my colleague might be able to help me.

DR. JONES: Just to add a little bit to that, I think you're trying to get a sense of what is the magnitude of underreporting. The answer is it's fairly variable. With all the newly approved drugs when they come out, people see bizarre reactions, and they report that to the FDA because

it's novel.

For something like this, where you have GI bleeding with an aspirin product, our sense is the underreporting is fairly significant because it's just not a novel event, and most physicians wouldn't think to report that.

DR. NIAK: One other thing. With GI bleeds and aspirin, it's become -- everyone is aware of it, so it's rare to file a report basically. As a practicing clinician, I could tell you if I see someone with aspirin and GI bleeding, I'm not going to report it to the FDA, although I should.

(Laughter.)

DR. SCHMID: My final question is you had mentioned that caffeine is suspected to stimulate gastric acid secretion that I thought Ms. Haysom this morning said that she disagreed with that. And maybe she can respond to this, that it wasn't necessarily caffeine, but it was coffee. And I was wondering if you could comment on that distinction.

DR. PARIKH: The article that was quoted, actually caffeine did increase hydrochloric acid

secretion, but the level of increase was not near what coffee and decaffeinated did, but there was increase.

DR. ROUMIE: Thank you. Dr. Solga?

DR. SOLGA: Hi. I just have a quick question about the antacid monograph from 1974. It says that all available data were derived from studies and experience with products in solution.

Forty-three years on, is there any reason to expect that any of this conversation would be changed if we were talking about the same products in a non-solution form? And is there any experience from abroad about these same medicines in a non-solution from?

DR. PARIKH: Can I defer that question to the panel?

DR. ADAH: Steven Adah, FDA. Your question was, again, is there any difference -- would we expect any difference? I don't think we've really gone back and looked at it, and I don't think we've had any reports to drive it.

DR. SOLGA: It just seems like a hold-over

from a 1974 monograph for all these years for, perhaps, no good reason.

DR. ROUMIE: Thank you. Dr. Choudhry?

DR. CHOUDHRY: Niteesh Choudhry, Harvard Medical School. I've got two questions, one is minor but just to clarify it.

The first, I think, for Dr. Parikh, is about duration. As I read the label, these drugs are labeled for -- the monographs talk about temporary relief. So I'm wondering if you could speak to your literature review and whether or not any of the studies -- do you have any information about how long people were taking the medications?

DR. PARIKH: Most of the literature has been mostly on chronic users. Some of the case reports that I put down on the slide, they were cases where consumers used the product for 2 to 3 days, sometimes 2 to 3 weeks long. But a majority of the data is not actually short-term sporadic use; it's longer term.

DR. CHOUDHRY: Great. My second related question is for Dr. Niak and perhaps also for

Dr. Parikh. I'm going to refer to Dr. Parikh's slide 12, which also appeared in the briefing document about the FDA concerns about aspirin-containing combinations. And the statement is that FDA continues to receive case reports of major GI bleeding events.

I just wanted to be crystal clear in my head that we're talking about the 1 to 3 cases per year that meet the case definition. And in those case definitions, do we know anything about duration?

DR. NIAK: Again, I'm sorry. Are you asking about the duration in terms of to start the medication or --

DR. CHOUDHRY: I'm asking both to clarify -- so on slide 12, I don't know if we can bring it up, Dr. Parikh's slide 12, FDA continues to receive case reports of major GI bleeding events. I think Dr. Parikh made the comment that the FDA is still concerned.

Notwithstanding the massive underreporting issues, I, as a practicing physician, also don't report these cases. But I want to know if we're

talking about the 1 to 3 cases; that's the basis for that statement. Secondly, if in those 1 to 3 cases we know anything about duration.

DR. NIAK: With regard to duration, I could tell you that the cases that I looked at, a lot of times some of the cases, it could just be after one dose, or it could be 2 to 3 days.

Again, some of these cases, they did have histories where there was a history of a GI bleed, or ulcers, or other medications. The maximum is like 2 to 3 days, and the minimum would be like after one dose.

DR. CHOUDHRY: Again, just to clarify that statement -- Chris, I don't know if you want to do that.

DR. JONES: I was just going to comment that to get back to the continued reporting, the answer is yes. It's not a lot of reports, but again, we've acknowledged or we believe underreporting could be significant for this.

DR. ROUMIE: Does the FDA want to respond?

DR. McCULLEY: Sure. I have an additional

comment. Out of these 20 cases, there are a couple of cases that dealt with misuse, abuse; there were a couple of patients that were addicted to the drug itself.

DR. ROUMIE: Thank you. Dr. Lipman?

DR. LIPMAN: Thank you. Dr. Lipman, from Washington. I just wanted to make the comment that I started earlier to make, which was that I've had the pleasure for many years to work with Dr. Hy Zimmerman who really developed the concept of therapeutic misadventure with acetaminophen and alcohol, that people were taking acetaminophen and alcohol and developed acute hepatotoxicity. I think he was chair of medicine at the Washington, DC VA when I was there and actually got me my first job there.

Second, I've got three comments if I can -- the second comment, if I can hopefully pronounce your name, Dr. Stergachis. I got it correct? Thank you.

The comment about changing admission policies for GI bleeding and hospitalization, this

is Dr. Lin's baby because he's the one who first pushed endoscopy, EI assessment of patients to keep them out of the hospital. So that's just a comment.

Third, I don't know if it's appropriate now or for later during our discussion, but in preparation for this meeting, I could not recall myself any instances of either GI bleeding or hepatotoxicity from acute use of combination over-the-counter products.

I asked all my colleagues at the VA, some of whom have been at other hospitals and as well as our fellows who rotate between the VA, Georgetown, and Washington Hospital Center, and specifically for GI bleeding or hepatotoxicity for OTC combination products. Nobody has seen anything.

We all know that aspirin is a major player, but we haven't seen this, and it's not just me and my dementia. It's my staff, colleagues who have not seen short-term OTC products causing GI bleeding or hepatotoxicity.

DR. ROUMIE: Thank you. Dr. Besco?

DR. BESCO: I appreciate Dr. Lipman's comment, but I also wonder -- I think Dr. Neill asked a very pointed question about self-study of appropriate selection by patients or products. And I know there weren't any for the hangover indication.

But I'm wondering if the agency or if any of the industry representatives were able to identify any published literature about patient comprehension regarding self-selection of appropriate combination products just in general that may help us understand how issues affecting consumer health literacy may be contributing to some preventable events involving combination products.

DR. MAHONEY: This is Karen Mahoney. No, we're not aware of studies to that effect, but that's a very good question.

DR. ROUMIE: Dr. Berlin?

DR. BERLIN: Roger Berlin, and this question is to Dr. Niak. The precipitant for this meeting was ostensibly a signal of GI bleeding associated

with aspirin and antacids, and we had a lot of discussion about it. But over 44 years, we see a total of 20 cases of serious GI bleeding reported at a fairly constant rate. And when you go to your appendix in your briefing book, which is appendix 3, table 4.3.1, just about all of the cases are confounded there, using concomitant NSAIDs; they have an underlying GI condition that would account for bleeding; they abused aspirin for up to a year.

In helping us to understand this signal, which you seem to associate as causal rather than coincidental, could you take a look, specifically with us, at that appendix table and show us which case or cases support the contention that there is a substantial safety risk that we should address?

DR. NIAK: I could answer this question later. I'll have to look at the -- or my colleague, Dr. Jones could --

DR. JONES: Sure. Your point is well taken. Clearly, spontaneous reports can be confounded, but given what we know with aspirin, its effects in the

GI mucosa, that's part of what's driving this. So we acknowledge there are not a lot of these spontaneous reports that FDA has received that we present here today, but I think that's not the only driver for why we're here. I think another driver is, is the combination of some of these products rational, based on what we know.

DR. BERLIN: If I might, I wasn't talking about the rationale for combination. I was talking simply about the data. And there's been a lot of supposition offered about the extent of underreporting and other factors, but when you look at the data that the FDA has put together, it is not necessarily compelling. And we're always talking about benefit-risk, so I think we should be clear about what the risk is before we begin the discussion of what the benefit is.

DR. NIAK: The issue is also -- a lot of these cases, there were cases where if a patient has histories of GI ulcers and GI issues, bleeding in the past, and the patient did not realize that taking this medication, this combination product

would be detrimental. The premise is that with the public, with OTC products, it can lead to that. So that's something to consider, certainly.

DR. ROUMIE: Dr. Farber?

DR. NIAK: I'm sorry. One other issue. As per my colleague, Dr. Jones mentioned already, the concomitant medications are -- like one patient for instance had received a renal transplant, cadaveric renal transplants and was on prednisone. And they didn't realize that they shouldn't be taking it, and they took it. So as the number of transplant patients increases, the risk is there.

Also, people who are on combination, other medications, poly-pharmacy with clopidogrel, warfarin, that could also potentially lead to that. We have a lot of patients who have atrial fibrillation who are taking medications which will cross-react with aspirin, so that also should be considered.

DR. ROUMIE: Dr. Farber?

DR. FARBER: Neil Farber, UC San Diego. A comment on the last discussion and then a question.

The comment is that basically that medications need to be generally safe and effective. And one of the articles that the FDA presented was the fact that basically patients who take combination aspirin and antacid have more GI symptoms than patients on placebo.

One would expect that, basically, if somebody were taking the combination, although they may have pain relief and not have a serious GI bleed, they might consequently also have some increase in GI symptoms as a possibility.

The question I have for either Dr. Niak, Dr. Parikh, or the FDA generally is, do we know anything about what the definition of overindulgence is, either by the FDA, by patients in terms of patient survey? I'm asking this because I'm wondering about overindulgence in drink, and are we actually asking the same question as hangover.

CAPT VIENNA: Hi. This is Mary Vienna. I gave the presentation on the monograph. The definition of overindulgence in food and drink is

not just alcohol. If you think about an experience, overindulgence in food and drink is what you feel after you eat Thanksgiving dinner. It's a very immediate, within 24 hours. It's resolved within less than 24 hours of the incident.

Hangover is the effect of overindulgence in alcohol alone and is that constellation of symptoms that was identified in the definition.

DR. FARBER: This is Neil Farber again. I recognize that's the FDA's definition. Do you have any data about patients understanding of what the label means, and is there any specifics about what overindulgence of drink means?

CAPT VIENNA: That's a really great question. One of the frustrations is that we don't have a lot of data on consumers' understanding of the term, and the advisory panel looked at it from a clinical perspective rather than a consumer's understanding. That's a good point.

DR. ROUMIE: Thank you. Dr. Solga?

DR. SOLGA: Dr. Solga. Following up with Dr. Choudhry's comments about duration, whether

we're talking about aspirin, acetaminophen, alcohol, or antacids, really, the safety is all about the dose and duration dependency.

For the same example of aspirin, 325 to 4000 a day, I don't care today. I do care if you take the same thing over, and over, and over again. Nobody's going to get into trouble in a day, and practically everybody is going to get in trouble long term.

From a regulatory standpoint, the package label has a daily dose ceiling. Has there been consideration for a weekly dose ceiling or a monthly dose ceiling to prevent recurrent treatment of chronic symptoms? I mean after all, that's really a difference between dyspepsia and hangover, is one is chronic and recurrent, and the other is presumably is less frequent. It seems like that's where most of the safety comes into play.

DR. ADAH: Steven Adah, FDA. There is a 10-day limit on use of these products. I mean so for just acetaminophen or aspirin in general, there's a 10-day limit. For hangover, it's

obviously to treat symptoms, so we would expect far less, or for overindulgence.

DR. ROUMIE: Thank you. Dr. Stergachis?

DR. STERGACHIS: Thank you. This is for Dr. Niak. Recognizing that FAERS really is a blunt instrument, even more so in the case of over-the-counter products, a commonly recognized event because it's in the label, et cetera. But nevertheless, labeling is one of our risk management tools.

Do you see any effect whatsoever of what the stomach bleeding warning may have had? Again, admittedly, these are small numbers, but before and after, just so we get an understanding of your perspective on the effectiveness of this particular tool.

DR. NIAK: I could give you two perspectives, one from the FDA's perspective and one from clinician's perspective. With regard to the FDA perspective, there can always be room for improvement, certainly. The labels are pretty good right now, but certainly, improvement can occur.

With regard to the clinician's perspective, I could tell you I have patients who -- with regard to overindulgence or hangovers, a lot of times, patients don't even -- they just want relief.

So the problem of maybe taking more so than usual is not even considered. A few cases were like that, and there are other medications, I've seen that happen as well. I hope that answers your question.

DR. ROUMIE: Dr. Lipman?

DR. LIPMAN: Yes. Just to comment to follow up to Mr. Berlin -- is it Dr. Berlin? I think there's a [indiscernible] of gastroenterologists, or internists, or clinicians around this table or in the audience who do not agree that aspirin increases the risk of GI bleeding and hasn't seen hospitalized patients.

I think the problem is we're dealing with unknowns. I try to present the our unknown, as my colleagues have not seen short-term use with combination products with excessive -- any episodes of hospitalization for GI bleeding. And I don't

think we're ever going to get better data, and so we're trying to make decisions based on what we know about long-term aspirin and translate this to short-term combination products.

DR. BERLIN: As a gastroenterologist also by training, I agree with the point. I was simply saying that the data is very thin that supports the contention that there was a specific safety signal associated with the aspirin/effervescent combination versus aspirin and NSAIDs.

DR. ROUMIE: Dr. Besco?

DR. BESCO: I apologize. I have my card up from my previous question. I don't have a question.

DR. ROUMIE: All right. Dr. Scarmezzi [ph], did you have a question?

DR. SCARAZZINI: Scarazzini. Hi.

DR. ROUMIE: Oh, sorry.

DR. SCARAZZINI: No worries. I'm in the same boat as Dr. Stergachis, right?

(Laughter.)

DR. SCARAZZINI: Greek and Italian. Anyway,

sorry.

I wanted to follow up on the issue of Dr. Besco's question about what do we know about where we stand from what is changed when we added the warnings to the label in this space.

Dr. Niak, this is really for you. You keep talking about several cases, many cases, one case, several cases. I'm just trying to get a good sense of, of those 20 cases, 8 of those cases, 8 of those 20 in that small number have been reported since the label has been updated.

We can talk about the label as much as we want, but that's what we have a mitigation tool at the moment. And especially in this space, it's important to make it as strong and clear as possible. Unfortunately, we don't have any way to know what the level of effectiveness is because we haven't really looked at it.

Of the 8 cases that you had since the label has been changed, did they differ at all qualitatively? Can we get a sense of it all -- particularly because the fatal case. You

also mentioned -- I'm sorry I don't know your name, but you also mentioned that you thought there was a case where a patient was addicted to Alka-Seltzer. I think that we should be careful about the way we're characterizing these cases with this limited amount of information.

My real question is, is there any characteristics of the cases -- you know, obviously, many things have changed. There've been alternatives; there are better labels and education from 1970 to 2017.

So since the label change, can you give us a sense of those 8 cases that have been reported since 2009, any particular root cause or any concerns in terms of what you've seen, or is the information so limited you can't tell us?

DR. NIAK: There were cases that alcoholism was involved, history of alcohol, and also history of GI ulcers in the past. Patients did have GI bleeding history. Also, concomitant medications were there, which basically patients who were taking NSAIDs; they were taking it. And also,

there were inadvertent uses of simultaneous aspirin and the combination products.

So the answer to your question would be, again, avoid concomitant medications with aspirin and other NSAIDs, if possible. Alcoholism certainly is a factor, and a history of GI bleed, upper or lower, can be considered.

DR. ROUMIE: Dr. Sanders?

DR. SANDERS: Lee Sanders, Stanford University. First, a comment, then a question.

Regarding some of the questions before around understanding of the labels and the medications, Dr. Besco's question, as a clinician and health literacy researcher, there have been a number of studies particularly, examining in my world, adolescents and young adults, picking up considerable misunderstanding of OTC products, including specifically acetaminophen-containing products. I'm happy to share that data.

Related to that question for the FDA folks, I think one of the FDA members before mentioned misadventures with misuse. I feel like we're

dealing with a huge gap here. We're dealing with the small N numbers of these adverse reported events, but the real population-wide experience in my world, adolescents/young adults, using these products -- the widely reported incidence of intentional and unintentional misuse of these products, particularly in concert with other prescription, non-prescription medications, and drugs of abuse. And I'm wondering, in the scope of this literature review, what you guys have discovered around intentional and unintentional misuse.

DR. JONES: Hi. This is Christopher Jones, FDA. I may ask Dr. McCulley to clarify. I know she mentioned something about misuse in a couple of reports. Perhaps it's a situation where someone said that they were addicted to the product. We clearly recognize this product doesn't have addictive properties.

Is that adequate?

DR. McCULLEY: That's true. I don't believe we've done any misuse/abuse studies on this

particular agent. There are about three cases in which somebody used 250 tablets within a week. There are a couple of other cases in which the patient admitted that they were addicted to the bubbles, or they like the taste of it, but that was the extent of it.

DR. ROUMIE: Dr. Mahoney, did you have a comment?

DR. MAHONEY: It was actually in regard to the previous comment about whether there was a change in pattern after the 2009 organ-specific warnings. That was actually one of the concerns that our OSE colleagues brought to us, is that despite the warnings, there wasn't a change in the pattern.

DR. ROUMIE: Thank you. Dr. Warholak?

DR. WARHOLAK: This is Terri Warholak, University of Arizona. I guess what I'm trying to wrap my head around, I totally agree that for long-term use, there's an issue. But I'm looking at the data, and from the 1970s on, we're having very, very few reports, and granted, of course,

it's a very, very small subset perhaps of what's happening. But it seems fairly consistent with a little bit of a blip at one point.

So I guess I'm looking for more background as to why now. Why are we looking at this issue now? It's for the FDA.

DR. MAHONEY: So the reason that the advisory committee was convened was because when we did the drug safety communication, we said that that would be our next step, was to have an advisory committee discussion of it.

DR. ROUMIE: Dr. Berlin?

DR. BERLIN: Yes. Roger Berlin. I don't know exactly to whom to address this question, but to the FDA certainly. I'm looking at the NSAID med guide for their prescription use, and the reason I'm looking here is because there were so many cases when people were on prescription NSAIDs and then got swept in this.

My question is what's your philosophy? I mean you can say that the OTC labeling is ineffective, but you could also say that the med

guide is ineffective because it doesn't provide specific warnings that are comprehensible enough for the consumers who use these products.

Maybe you can share the philosophy of how you fix the understanding. Is it just on the basis of the OTC label, or do you need to go back and look at the way you communicate to the patients with these medication guides?

DR. MAHONEY: This is Karen Mahoney. As the committee probably knows, there are two ways that over-the-counter products are regulated. One is the type of products that are under discussion today, which are under monograph. But there are also products that are marketed under new drug applications, the same way as prescription products are marketed.

For new drug application products, they must come to us with an application prior to marketing the drug. In those circumstances, we request label comprehension and often other types of consumer behavior studies. So we have the ability to get a lot more information on NDA products than we do on

monograph products.

For the monograph, our ability to compel companies to do the types of label comprehension studies that could inform what types of labeling would make a difference, our ability to get that is very limited.

I should also say that products that want to market under the monograph but don't appear to be eligible for marketing under the monograph, they can still gather the data and submit an NDA application.

DR. ROUMIE: Are there any other clarifying questions for the FDA?

DR. SMITH: Tommy Smith, Manchester University. This is for Dr. Mahoney.

You had indicated that it's challenging to have labeling changes for OTC products that were brought in under a monograph, but it was my understanding that for OTC products, they have to be labeled with adequate directions for use.

Does that term encompass patient understanding and being able to use the drug in a

safe way, in a way that will make the drug as effective as possible? Could you clarify that gap there for me, please?

DR. MAHONEY: Yes, products that are marketed under the monograph are expected to have adequate labeling. As Captain Vienna presented, we have a big challenge in our ability to change a monograph because of that extensive three-part notice and comment rulemaking process. So it is challenging and can take years.

DR. SMITH: If those products are being used in unsafe ways and patients don't understand how it is to use it, then are those products no longer labeled with adequate directions for use?

DR. MAHONEY: I find it to be a little bit of a difficult question to answer, but what I can say is that because of the challenges in changing labeling through rulemaking, the FDA takes other approaches.

For example, in this case, we use the drug safety communication. And sometimes we provide guidances where we will indicate that it is

acceptable for sponsors to use different labeling than what is under the monograph while we're attempting to change the monograph.

I would like to be sure that I do answer your questions, so is there more to it?

DR. SMITH: It just seems to me then because of this challenge, there are OTC products on the market that are, in fact, not labeled with adequate directions for use as the law would seem to allow.

DR. MAHONEY: I will say that there are some monograph products for which we have some safety concerns and for which we are trying to get rulemaking to go through. I guess the answer would be probably yes, but we are attempting to get those rulemakings done.

In the interim, we have these other measures like drug safety communications to let the public know and also guidance to permit manufacturers to make labeling changes while the rulemaking process plays itself out.

DR. ROUMIE: Thank you. Dr. Besco, last question.

DR. BESCO: Kelly Besco, OhioHealth. This is for my own general knowledge. Part of my suspicion about patient comprehension ties into the use of brand name extensions. And just for my own clarification, if an over-the-counter product falls under a monograph, then FDA has no authority on the initial naming of the product; is that correct?

DR. MAHONEY: The name does not come to the FDA for review prior to marketing.

DR. ROUMIE: We will now break for lunch. We will reconvene again in this room, in one hour from now, at 1:00 p.m. Please take any personal belongings you may want with you at this time.

Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any members of the audience. Thank you.

(Whereupon, at 12:01 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:01 p.m.)

Open Public Hearing

DR. ROUMIE: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with industry. For example, this financial information may include industry's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of the statement, to advise the committee if you do not have such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee places great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record?

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I

am senior fellow at the National Center for Health Research, and I previously trained at Johns Hopkins University School of Medicine.

Our center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from the pharmaceutical industry, so I have no conflicts of interest.

Like many public health experts and advocates, we are very concerned about treatments that are marketed and promoted for hangovers that contain either acetaminophen or aspirin. Both acetaminophen and aspirin have well-known health risks, particularly when consumed in conjunction with alcohol. Acetaminophen can cause liver damage, and aspirin can cause stomach bleeding.

The FDA's review points out that most research indicates that moderate alcohol consumption may be associated with a higher risk of acetaminophen-related adverse events, including liver toxicity, and unfortunately, substituting other nonsteroidal anti-inflammatory drugs is not

any safer.

Consumers are likely to take pills for hangover shortly after, just before, or even during alcohol use. Since these are over-the-counter drugs, most consumers assume they are completely safe and are unlikely to read warnings about the risks.

Adolescents and young adults may be at particular risk for the cumulative effects of binge drinking paired with analgesic consumption because they are even less likely than adults to read the label carefully or be cautious about avoiding possible adverse events. They are unlikely to realize that they are drinking heavily enough to be at risk.

We work closely with patients and consumers, and we know that many are unaware of all the ingredients in over-the-counter combination products that they use, whether they are for hangovers or colds.

As the FDA noted, research indicates that most acetaminophen overdoses are unintentional or

due to the failure to recognize the risks. For example, unintentional overdoses can occur when a consumer does not realize that acetaminophen isn't a hangover medication and additionally takes acetaminophen or aspirin to treat or prevent a hangover.

FDA's standard for drug approval is at the benefits of taking the drug for that indication must be greater than the risks. There is well-documented evidence citing the risks of consuming alcohol and these drugs around the same time. A person who has been drinking enough to expect a hangover or to already have a hangover is likely not in a condition to carefully read the label of an over-the-counter medication.

The FDA should base its decision on how to label antacid/analgesic combination drugs on scientific evidence, and scientific evidence clearly indicates that the combination of alcohol with these drugs can be dangerous. The bottom line, medication should not be labeled for hangovers if they contain ingredients that can

cause serious harm when taken before, during, or within a few hours after drinking alcohol.

These are the key issues that the FDA should address:

One, antacid/analgesic combination over-the-counter medications that are marketed and sold for hangovers should not contain acetaminophen or aspirin. Ideally, the label should clearly say that the reason they do not include these types of pain killers is because of the uncommon, yet potentially very serious risks of combining them with alcohol. Antacid/analgesic combination drug label should clearly indicate that acetaminophen or aspirin are active ingredients.

Two, all products with acetaminophen or aspirin should have warnings that they are risky to use for hangovers because of the risks of taking these analgesics before, during, or within a few hours after consuming alcohol.

If it were possible to include a clear description of under what circumstances, for example, the number of drinks, the length of time

following alcohol consumption, et cetera, alcohol increases the risks of these drugs, that would be best to include, but we don't seem to have that information available at this time.

Three, the labels on aspirin and acetaminophen currently have warnings about their risks for individuals who consume the drug and 3 or more drinks every day, which implies the risk of long-term use of alcohol and these analgesics.

The FDA should modify these warnings to also include one episode of heaving drinking. It is important to keep in mind, however, that many people do not consider 5 or even more alcoholic beverages in a short time to be binge drinking or heavy drinking.

Rather than warning consumers the current labels for over-the-counter treatments for hangovers, instead encourage consumers to use these treatments around the same time that they are consuming large quantities of alcohol, we encourage you to strongly urge the FDA to focus on patient safety by removing the treatment of hangovers from

the label of any medications containing aspirin and acetaminophen because the risks outweigh the benefits. At the same time, we urge the FDA to issue a press release and host a press advisory phone call to publicize their concerns. Thank you.

DR. ROUMIE: Thank you. Will speaker number 2 step up to the podium and introduce yourself? State your name for the record and any organization you are representing.

MR. SPANGLER: Good afternoon. I'm David Spangler, with the Consumer Healthcare Products Association. We represent manufacturers of non-prescription medicines. We have over 80 manufacturer members, including Bayer and Rally Labs, however, I'm an employee of CHPA, not them directly.

There were a number of questions or assertions that came up this morning around monographs and the pace to change labels, so I just wanted to make a couple of comments on that topic.

As Dr. Mahoney pointed out, there are some workarounds; there are opportunities to do

voluntary label changes ahead of rulemaking. I want to point out three instances where our industry has led initiatives to change labels voluntary.

First, a number of years ago, we began highlighting the word "acetaminophen" in the active ingredients section of all products with acetaminophen since, as has been pointed, it is in so many products. That was ahead of an FDA rule that came several years later.

Second, in pediatric cough/cold, a number of years ago, we changed labels after it was drawn to folks' attention that there had been a number of serious adverse events in young children, particularly for an unsupervised accidental ingestion to say "Do not use under 4" and to say "Do not use to sedate your child" in the case of an antihistamine.

Third example, a more recent example, the industry led an initiative to change from 2 concentrations of pediatric liquid acetaminophen to 1 concentration of pediatric acetaminophen liquid

to reduce the risk of dosing errors.

Those are just three instances where ahead of government action, industry has stepped up to change labels voluntarily.

I think all these instances and some of the comments and questions that came up point out the need for a better system to change labels expeditiously when there's a need to make a safety-related label change. And it's for that reason that we are currently lobbying the Congress to do a number of reforms, including to make safety label changes more efficient before Congress. Thanks.

DR. ROUMIE: Thank you. The open public hearing of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Dr. Pratt will now provide us with the charge to the committee.

Charge to the Committee - Valerie Pratt

DR. PRATT: Good afternoon. Now, I will provide the charge to the committee and introduce the questions for discussion.

The key points discussed today include the following: antacid/analgesic drug products containing aspirin or acetaminophen are currently marketed for upset stomach and hangover indications.

The combination of antacid and aspirin for use in relieving gastrointestinal symptoms has been a point of comment regarding safety throughout the rulemaking process. Bleeding is a known risk of aspirin therapy, and 21 CFR 330.10(a)(4)(iv) requires that OTC drug combinations provide rational concurrent therapy. Concern persists for these products. A drug safety communication on this topic was released in June 2016.

On December 24, 1991, a tentative final monograph was published that amended the antacid and internal analgesics monographs to add indications for antacid and antacid/analgesic

combination drug products. These amendments are part of a larger effort to establish a separate monograph for overindulgence, which allotted appropriate indications related to relief of such symptoms to the related monograph categories.

As a result, the issues discussed today touched upon four separate monographs: the internal analgesic, antacid, overindulgence, and stimulant monographs. The upset stomach and hangover indications are interwoven. One cannot address one without affecting the other.

Regarding hangover, its definition is lengthy and symptom-based. The advisory review panel on OTC miscellaneous internal drug products concluded that no clinical studies were necessary to demonstrate effectiveness in treating hangover.

In 2009, the organ-specific warning's final monograph required new labeling for acetaminophen, which included warnings to highlight the potential for hepatotoxicity, which is also associated with alcohol use.

The agency is concerned that current

monographs permit the sale of combination products containing acetaminophen for indications related to hangover. Our review identified acetaminophen/caffeine products but no acetaminophen/antacid products currently on the market for hangover indication.

With the previous presentations and the key points in mind, we ask you to consider the following questions:

Question 1 for discussion. Discuss the safety of the use of OTC analgesic combination products for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea.

Question 2 for voting. Is the combination of an analgesic with antacid a rational combination for over-the-counter use for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea?

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 and excessive alcohol ingestion. The monograph states that the symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pain, headache, dullness, and/or depression or irritability.

Question 3 for discussion. Discuss whether or not the treatment of hangover is an appropriate indication for OTC drug products. If the hangover indication is appropriate, which ingredient should 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. Thank you.

Questions to the Committee and Discussion

DR. ROUMIE: This is the portion where we will start with the discussion in point 1, which is the discussion of the safety and over-the-counter analgesic combination products. The particular focus here is safety and the combination products.

Anybody want to kick it off? Yes?

DR. MAHONEY: If I may, I'd just like to make a few comments about some things that came up in the clarifying questions.

DR. ROUMIE: Sure.

DR. MAHONEY: The first thing I'd like to talk about is the fact the data are sparse, and we know that. But that was just the beginning of the discussion. When our pharmacovigilance colleagues brought this to DNDP, and we had our discussions about this, multiple people asked, why is aspirin in something that's intended for an upset stomach?

Then as we progressed with this, we realized that the monographs encompassed hangover and were quite extensive. Again, we asked this question of why is there aspirin or acetaminophen in something

intended to treat hangover, and maybe why is there caffeine in something intended to treat a hangover?

That concept of rational concurrent therapy, I would like to clarify something about that. The word "rational" in this sense is part of a regulation. When one hears the word "rational," you think, oh, rational means of sound mind, and irrational means maybe having mental illness or something like that. But in this circumstance, it comes directly from a regulation that says that if you combine two active ingredients, that combination has to be rational concurrent therapy for the therapeutic indication.

That is a very important question for us, and that's something that we really want to hear the committee's thoughts on, the concept of whether these particular combinations of active ingredients represent rational concurrent therapy.

I'd like to make another couple of points. Just one moment. I had to make a couple of notes. Pardon me.

Another thing that I want to make clear is

that the original monograph panels were not comprised of FDA personnel. They were comprised of external clinical experts who gave input based on their clinical knowledge in that therapeutic area.

These recommendations were made a long time ago, and science has progressed greatly, and in particular, not only clinical science but also our understanding of how important consumer comprehension is. That's another point I wanted to make; how long ago it was and also just, by the way, that these were not FDA experts.

One of the committee members asked whether there are efficacy data, particularly for the hangover indication. That is an important question because when we don't have adequate information on efficacy, when we try to do a risk-benefit analysis and we don't have the efficacy information, there's only risk. So we can't do a risk-benefit analysis, which is really important for us in determining whether or not a product should be marketed.

A final point is that the internal analgesic and the overindulgence monographs are not final

monographs. When you saw the rulemaking process, they're at the second place where there's a proposed rule and a tentative final monograph.

So there is still a need for information to help the FDA make its decision and write that final monograph. The input that the committee gives us today will be very beneficial as we attempt to finalize those monographs. Thank you very much.

DR. ROUMIE: Thank you. I'll kick off the discussion with the notion, even though this is part 2, about the combination being a rational combination. I often think of this as if a patient were to call my office and say, you know, I have an upset stomach, would I feel okay with this kind of recommendation, go use this product over the counter.

To me, I do not see this as a rational combination because I often would not treat an upset stomach with aspirin products. I understand the clinical experience and the potential underreporting, but I don't think that the two products together for that particular indication is

one that is rational.

Yes? Dr. Smith?

DR. SMITH: With regard to the term "rational," that's really a regulatory term of art, if you will. A rational relationship is a fairly low hurdle to clear as compared to a compelling relationship or a significant relationship. I think we have to remember that we could draw a rational relationship between most anything. So I think it's important to remember that that really is a very low bar.

DR. ROUMIE: Dr. Lipman?

DR. LIPMAN: I'm not sure where I'm going to go with this. But if you look at question 1, the first part, relieving minor aches and pains, I don't think that minor aches and pains can be relieved with just an antacid.

The other thing is that I am sure that most practitioners in this room, if you could reduce the number of patients in your office with intractable heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea, you'd say,

hallelujah.

These are useful products. Bayer, it sounds like they're going to just the antacid product without a combination. I think we need something, and I think the way this is formulated, minor aches and pains really aren't associated with heartburn, et cetera, et cetera, et cetera. They're separate.

So if you're going to have two separate things, then you're going to have to have two separate ingredients. If you're not going to have two separate things, then you can have a --

DR. ROUMIE: I get it, and it's complex because the problem is we're discussing the combination of agents, and the combination of agents touches on four separate monographs. And we're talking about ingredients that fall into four separate categories. But we're tasked with understanding the safety and the rationale behind the combination of two agents. So I get it. It's complicated.

Dr. Solga?

DR. SOLGA: I'm speaking as a

gastroenterologist, and I invite comment from the other gastroenterologists on the committee and/or, if the chair allows, Dr. Lang [ph], one of the world's experts on peptic ulcer disease.

I don't mean to be provocative, but I wish to state that aspirin really doesn't cause bleeding; it potentiates bleeding. Aspirin causes ulcers. Routine use of aspirin over time causes ulcers through the decreased prostaglandin synthesis mechanism. That is completely different than decreased platelet aggregation, which can potentiate bleeding that's occurred.

So when we talk about these 20 cases through the literature, all of these folks would be expected to show up with gastrointestinal pathology the night of their binge, and then they took aspirin, and then aspirin may have potentiated their bleeding. So it's a duration issue.

It's a duration issue, and I think that's really quite important. Dr. Warholak asked the question about different patient errors and points in time. Well, patients today are very different

than patients as they used to be. We take more NSAIDs or take more anticoagulants. We have helicobacter pylori. We're on more PPIs.

Things have really changed a lot, but the overnight brief use of aspirin is not going to cause bleeding. It may potentiate bleeding. There's an important distinction.

DR. ROUMIE: Dr. Smith? No? Okay. Dr. Besco?

DR. BESCO: Kelly Besco, OhioHealth. To build upon what Dr. Roumie was talking about, the fact is, as a clinician, you could say, well, you have a stomach issue; go get some Alka-Seltzer. But Alka-Seltzer could be a myriad of products depending on the patient's understanding of what is in the different types of Alka-Seltzer brand name products.

I think we need to think about that too in that the brand name extension liberties that are permitted for a particular company to use can also be very confusing for a patient to know exactly what product they're supposed to select when going

to the pharmacy to pick up something that will treat their condition.

DR. ROUMIE: Dr. Farber first.

DR. FARBER: Neil Farber, UC San Diego. I have several concerns about this combination product. I'm not a gastroenterologist; I'm a general internist, but I've seen a lot of patients in my career who have taken NSAIDs, including aspirin, had erosive gastritis with bleeding, didn't have ulcers. So I think we know that occurs.

In addition, the product, even though it has an indication of relieving GI symptoms, it has shown to be a cause of GI symptoms when viewed against placebo. Therefore, I think that's a problem.

The last problem I see is one in which there may be confusion on the part of the public in terms of some of the labeling, for example, like what overindulgence means and whether one takes it because of an overindulgence, one takes it because overindulgence in alcohol with hangover. There may

be confusion, and we don't know what the public is thinking about this. For those reasons, I think there are some problems with it.

DR. ROUMIE: Dr. Wishingrad?

DR. WISHINGRAD: Marc Wishingrad. I also have problems with the combination product, but I'm not really concerned that there's a risk of very short-term use of these things.

I think, as other people have said, that confusion about how these products are supposed to be used is the major issue. People may be taking these more often, many times a week, or for months, and months, and months. And that's the problem. There are now dozens of products for GI upset, for stomach problems.

When these products first came out, they were just antacids, and now they're H2 blockers and PPIs. And I think the big problem is the confusion with how to use them, and people are going to be taking much more aspirin than they know they're taking over a longer period of time.

DR. ROUMIE: Dr. Choudhry?

DR. CHOUDHRY: Niteesh Choudhry, Harvard Medical School. I just wanted to pick up a little bit on what Dr. Lipman was saying because I think agree with him.

The confusion here, as Dr. Pratt kind of alluded in her charge to us, comes from the idea that upset stomach and hangover are linked through a series of updates. If we were to, for a second, separate these two ideas and say, okay, if we're going to treat upset stomach, does it make sense to combine these drugs, does it make sense to treat hangover with a combination product, I think we might come to different answers.

So to the extent that when we get to this, we are allowed to draw that distinction, which admittedly may be somehow regulatorily challenging, I think that's a useful idea. That doesn't solve the problem of patients being able to understand what they're taking it for or some of the stuff about what patients perceive as being a hangover cure and brand names sort of hold over, but it does sort of begin, at least, distinguish what entity

we're treating, which I think we're conflating by putting these two things together.

DR. ROUMIE: Dr. Wu?

DR. WU: I appreciate the discussion. I think two points that I'm struggling with, one, I get that the label is for a short duration of period, 24 hours of use. However, oftentimes, patterns in behavior emerge, and people will often will use these much longer than just 24 hours, or if it's heartburn issues, or even if it's hangover, there will be folks that will have hangovers more than just one day in a week.

So there are real challenges, I think, with thinking about the duration as labeled versus the duration and practical use combined with changing consumer demographic and consumer behavior where concomitant use has become much more prevalent of other NSAIDs, other analgesics.

As I read the question, I think it is a distinct point that talks about the use of over-the-counter for the relief of minor aches and pains associated with heartburn, sour stomach. So

it's really this connection of the two. From both patient experience, and from friend experience, and even myself, I think when you have minor aches and pains, oftentimes, you use NSAIDs for one thing, but you might take Alka-Seltzer for your stomach.

So I think there's just a real challenge when we're thinking about this as a short-term indication where consumers, because their behaviors are changing and their likely multi-drug use across many different categories, I struggle with that concept of whether this is rational or not to think about treating pain that's associated specifically coming from a GI distress. That's where I'm sitting right now as I think about the question.

DR. ROUMIE: Thank you. Dr. Aldrich?

DR. ALDRICH: Dawn Aldrich, SOLUTIONS Cancer Resource Center. I represent a community where there are certain cultural practices. If they are told or if they believe, in the minority community, ginger ale is like the elixir for everything, ginger ale and Vicks, that'll cure everything.

If someone is under the impression that

taking these antacids would be helpful for them, that's something that they will take. In addition to that, if they have a headache, then they'll grab Tylenol. And none of this is being, in a sense, rational in terms of what we're talking, but in their own minds, this is something that they feel would take care of each thing.

So I think this is something that is a good topic to discuss, and I think it's something we need to consider in terms of bringing these things into products and mixing them where people are not really even sure what's in there.

DR. ROUMIE: Dr. Engle?

DR. ENGLE: Jan Engle. I really struggle sometimes with combination products. I mean, many times they fill a really good niche for our patients. But other times, I think they're confusing, and this is one of the cases where I really think it is.

If a patient presents to me, and he or she has an upset stomach or heartburn or whatever, there's better remedies than one of these

combination products, especially with aspirin in it, which can confound the whole clinical picture because aspirin can upset your stomach, I mean bleeding, yes, and all that.

I would not recommend this for somebody with an upset stomach because we have better remedies for that. And maybe have to use two separate products if they also have aches and pains because I may recommend acetaminophen in that case.

The other thing that nobody has talked about that concerns me with these products is the massive sodium load that you get with these effervescent products, including Blowfish. To me, this is just not a good solution for most of our patients.

DR. ROUMIE: That was some of my point at the beginning, which is, would I, as a clinician, say to somebody, go get an Alka-Seltzer over the counter, or would I say, go pick up a PPI, and I'll see you next week and figure out what's going on.

I think the times have changed since these drugs first came out. The data has changed. Our knowledge has changed, and I think need to evaluate

basically the history of how this came about, but also what do we know now, is this the way we would practice now.

Dr. Sanders, and then Dr. Baron?

DR. SANDERS: Yes. I just want to confirm some of the sentiments before. As a pediatric clinician who takes care of children, adolescents, and young adults, I'm very concerned about the confusion that this begets among that population and the potential problems for safety for the use and misuse by adolescents and young adults, as I mentioned previously, but also by younger children in the household.

Oftentimes, these products are purchased once but then used repeated times in the future for other indications, and it offers a lot of confusion to many families, including where I practice, lots of families with limited literacy, limited English proficiency, underrepresented minority communities. It offers a lot of confusion, and I think through that confusion, problems for safety.

DR. ROUMIE: Dr. Baron?

DR. BARON: Elma Baron, from Case Western. I'm simply looking at the individual questions at this point. I think for question number 1, regarding the safety, based on the data that we have seen -- and we can have a lot of assumptions, but the current data is the current data. I do not see an overwhelming concern about the safety based on a number of cases of adverse events reported.

However, going to question 2, I think I do resonate with a number of people in this room that the combination does not seem to represent best practice at this point in time.

DR. ROUMIE: Dr. Lipman?

DR. LIPMAN: Dr. Lipman from Washington. I like what Dr. Baron said, but I would like to go back to my point and ask for some other comments, that people could agree or disagree, that minor aches and pains really are not usually associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea. They're separate symptoms.

Another thing is I don't think there are

very few clinicians in this room who would tell a patient take one of these over-the-counter products. But these over-the-counter products are supposed to there before they see them, not as our recommendation for their use.

DR. ROUMIE: So that's even more important that they must be safe and effective.

DR. LIPMAN: Well, I don't hear anything that says they're not safe. And if people are buying them, they must consider them effective. For the functional symptoms, if it works, great, because lots of things don't work for functional symptoms. A lot of PPIs that are prescribed are inappropriately prescribed. I mean if they call you, and you belch, and you get a prescription, you tell them to get a PPI; that's inappropriate.

The question is can this be reworded, but as long as you have minor aches and pains, I think that's different than everything else.

DR. ROUMIE: Dr. Stergachis?

DR. STERGACHIS: Andy Stergachis. I got little really to add to what's already been said.

The notion of minor aches and pains, along with these GI symptoms, it doesn't make sense to take aspirin if you have GI symptoms. And I haven't heard anything supporting the use of combination products for the indication here. There are safer alternatives, including not taking aspirin at all, or for that matter, any other NSAID if that's the combination of symptoms.

DR. ROUMIE: Dr. Smith?

DR. SMITH: I have both a question and a comment. My question is the language that we're supposed to discuss and ultimately vote on, minor aches and pains associated with heartburn, sour stomach, et cetera.

I'm looking at the language in the overindulgence monograph, which includes hangover, and I don't see this exact language listed here in the definition of hangover or in the other notes from the monograph. My question is, where does this language come from?

DR. ROUMIE: I'll ask the FDA. Is that the separate discussion of point 3, or would you like

to clarify?

DR. ADAH: We can clarify. Steven Adah. That language, first off, is selected, meaning it says you can -- there's certain language that says there are these three indications, plus additional indications you can add.

These things are also covered in the internal analgesic monograph and in the antacid monograph. If you also look in there, you might see them. So that's why we're discussing the conglomeration of all these monographs because the language is crossing over many.

DR. SMITH: The term "hangover" is incorporated into this language?

DR. ADAH: Hangover is in the overindulgence monograph. It's specifically listed in there, but some of the other indications that we're looking at are also contained in the other monographs.

I'd refer you to the table that Captain Vienna presented briefly, and it's in the briefing package, where it shows where the various language shows in the different monographs, and

that may be the best place to look.

DR. SMITH: Then my comment, I certainly agree with the clinicians around the table, talking about better choices of medication to use, but that isn't what our charge is with regard to question number 2. It's essentially much more narrow than that.

Is there a rational relationship between the use of the analgesic along with the antacid? Is it rational? Not, is it the best practice? I think we have to remember what our question is.

DR. ROUMIE: Thank you. Dr. Schmid?

DR. SCHMID: Admittedly, I'm probably speaking as the general public here since I know very little about this clinically. But it seems to me if you had -- I can see if you just have symptoms of GI and you have no pain, that we probably don't want people taking a combination product that had aspirin in it. However, if you did have both, and if you, for example, took the new form of the bioproduct that just has an antacid, but you knew it didn't have pain relief in

it, a person might just take an aspirin because they've got a headache or they've got pain.

So I'm wondering if we decouple these, what are people really going to do. I think they're still going to take these products. I think most people would think it's rational to couple a pain relief product with a GI symptoms product, if that's what they have.

I'm just asking as a non-clinician here, how would you respond to that.

DR. ROUMIE: I would say personally that even if you chose to take a separate pain relief product, there would be less likely an overdose or a therapeutic misadventure because you're consciously taking two of one pill and then two sodium bicarbonate products, and you're not unintentionally taking two extra strength aspirin, plus an Alka-Seltzer Plus or Extra Strength, which also has 1000 milligrams of aspirin, and now I've just taken 2000 milligrams.

So I think this happens, and this discussion often comes up when we talk about combination

products because many people don't know that a combination product is a combination regardless of labeling.

Dr. Solga, you had a --

DR. SOLGA: I agree with both of you. I got done saying earlier, aspirin doesn't cause bleeding; it potentiates bleeding. I also think that in the short-term, it's a very sensible remedy for minor aches. It causes chronic gastroenteritis, which is, by definition, something that takes time. It doesn't immediately cause any GI symptoms that a dose or two that are going to be meaningful.

The question that we're talking about with the coupling or uncoupling is, okay, person wakes up with a hangover, is it a GI upset predominant hangover, a minor ache and pain and headache predominant hangover, or both? Do we want to afford them the possibility of just getting out of the question of taking a single medicine rather than thinking through each one of them? And I'm not sure anybody waking up with a hangover is

really going to think about that that clearly. I don't believe it.

DR. ROUMIE: Okay. I will read the first question into the record, and then I'll summarize.

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

Many of the points that have come up during the discussion predominantly falls into a couple of different categories.

Number 1, duration of use. The issue is related to a higher dose than what patients recognize they are taking and chronicity of use. That leads to point number 2 that was brought up, which relates to patient understanding and a need for patients to think through and read through the drug facts label, which is somewhat unclear at times and has daily limits of dose and not necessarily long-term. Even though it says it's for a short duration, sometimes patients don't

follow through with that, and sometimes it's a lack of understanding.

Issues were brought up related to the potential sodium load for other patients with other conditions, such as heart failure because it's a pretty good shot of sodium.

There were issues that were brought up that related to use and reuse in household, apparently potentially for children and for others who may not have appropriate indications.

The other big issue that has come up was the separate and maybe very weakly associated symptoms of aches and pains with the gastrointestinal symptoms and that maybe those two are not linked.

Any other comments? Yes, Dr. Farber?

DR. FARBER: Neil Farber, UC San Diego. The other thing is regarding the effectiveness, which I know is not listed in question 1 but was discussed to some degree. I have concerns about a drug that has an indication for a particular symptom, which actually shows decreased effectiveness based on some of the data.

The other thing is just because somebody buys a medication and uses it doesn't mean it's effective vis-à-vis the number of over-the-counter herbals, et cetera, that purport to do all kinds of things that don't.

DR. ROUMIE: Have we covered all the issues? Dr. Mahoney? Dr. Pratt? You're good?

DR. MAHONEY: Yes.

DR. ROUMIE: Okay. We will move to number 2, which is a voting question.

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?

Here, I'd like us to have just a little bit of a discussion before we turn on the electronic voting. Should we discuss rational use, the combination of the drugs or --

Dr. Lipman, you have a comment or a concern?

DR. LIPMAN: Yes. I don't like combination drugs. I don't think they should be taken. I

don't think they should be used. Unless the FDA is willing to eliminate all combination drugs, I'm not sure that we should be saying this combination is bad and then let other committees decide whether other combinations are good or bad.

I'm going to have problems with this because I think that this combination is not rational, but I'm not going to vote against it, until I hear something more compelling.

DR. ROUMIE: One of the things that -- again, this is the complexity of the monograph process, which is there are ingredients on the monograph, and the one CFR regulation that they referenced was two things can be put together that may be from separate monographs, if it's a rational combination.

So the question is, is this a rational combination? Dr. Baron?

DR. BARON: Elma Baron from Case Western. May I request a repetition of the definition of "rational" in this instance?

DR. MAHONEY: Captain Vienna, do you have

that available?

CAPT VIENNA: I can read you the combination regulation. The regulation itself does not define rationality, but within the context of the regulation itself, you might find some guidance.

Let me just go back and take a look here. "An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect, when combining does not decrease the safety or effectiveness of any of the individual active ingredients, and when the combination, when used under adequate directions for use and warnings against unsafe use, provides a rational concurrent therapy for a significant proportion of the target population."

That's the policy. That's the regulation. It does not define "rational" in the regulation.

DR. ROUMIE: Dr. Besco?

DR. BESCO: I'm just wondering if it would be of value to have two separate questions to vote

on, one related to aspirin and one related to acetaminophen.

DR. ROUMIE: I was told at my first meeting ever that when I attended, don't change the question.

(Laughter.)

DR. BESCO: Don't change the question.

DR. ROUMIE: We only get into problems when you change the question.

DR. MAHONEY: This is Karen Mahoney. We do ask that the committee vote on the question as written, but we welcome all qualifying comments and so forth. But we do ask that you vote on the specific question as written.

DR. ROUMIE: Okay. Dr. Farber?

DR. FARBER: Neil Farber, UC San Diego. Hearing that definition, at least with aspirin therapy, there is a decrease in effectiveness of the GI component if you give aspirin, and that's been shown, not in terms of risk but in terms of symptoms. Those patients who had the combination had more GI symptoms than patients with placebo, at

least in one study.

From that perspective, at least as aspirin is concerned, that in and of itself indicates that basically this is not an acceptable drug.

I still also have a great deal of concern about the way the labeling is and the fact that basically patients can get very confused with it, use it inappropriately, perhaps put themselves at risk.

DR. ROUMIE: Dr. Smith?

DR. SMITH: The regulatory standard in applying the term "rational," in looking at this, minor aches and pains, analgesics would be appropriate therapy for minor aches and pains, and then heartburn, sour stomach, et cetera can certainly be treated with an antacid product.

We haven't seen compelling enough data to show that if a user takes this as labeled, which is short-term therapy, that even aspirin and acetaminophen would make the product more risky, if you will.

DR. ROUMIE: Dr. Besco? Nothing.

Dr. Stergachis?

DR. STERGACHIS: Andy Stergachis. Reflecting even further on the definition of "rational," thank you very much, given the combination, one active ingredient, in this case from knowledge of mechanism of action and some data, increased the risk of GI bleed.

So I, for one, am looking at this as a way to manage benefit-risk beyond label and will support a vote that is in the direction of non-supporting the combination for reasons cited.

DR. ROUMIE: Thank you. Dr. Schmid?

DR. SCHMID: Chris Schmid. Brown. I can see in the case where an antacid is sufficient, that giving the analgesic would not because useful because it could increase the GI symptoms, and it's not going to give you any benefit. But if you have both pain and upset, then it would seem that even if the aspirin increases GI symptoms, it might reduce the pain enough that the overall benefit would outweigh the risk.

I'm also wondering, in the question, it says

"an analgesic" and we've mentioned aspirin/acetaminophen, are there other analgesics that are considered that wouldn't have these issues? Because the question is very general.

DR. ROUMIE: Thanks. I'm just going to remind everyone, we will do voting in a minute, so do not state your vote just yet.

Dr. Choudhry?

DR. CHOUDHRY: Niteesh Choudhry. Harvard. I think we can all agree that there's very, very limited data. I'm struggling a little bit with some of what Dr. Farber has offered in terms of whether we actually know that the efficacy of the combination product is less by adding aspirin or not.

There's an endoscopic study that's in the briefing materials. There are a few allusions to individual patients who may have tolerated the combination as well. There's not a ton of data about the non-combined product either.

So there's, to me, no doubt questions of efficacy, but not to the point that we know that

the combination is less effective than the parent drug by itself.

From that perspective, if we are using rationality, and rationality based upon a lack of equivalent efficacy to the two drugs taken separately, I'm not sure we've met that standard with what we've seen today either.

DR. ROUMIE: Dr. Neill?

DR. NEILL: One of my first NDAC meetings, the topic was handwashing, and I thought I got this; I've been washing my hands a long time. And I learned what I didn't know about handwashing.

Now, 18 years later, this meeting is announced, and I think, as a Kentuckian, familiar with bourbon, I've got this.

(Laughter.)

DR. NEILL: We're discussing the nuance of one tentative final monograph language decision of three, each of which have taken an aggregate more than 40 years to get where we are now, and in the absence of any data, about whether consumers can self-select or understand, or make a safe decision

to choose an effective treatment for what most of the clinicians here know is going to be treated with recrimination, don't do that again.

What I tell my patients is, when they come in, they say, you know, this is what happened. And I said, wait a minute, so you drink a fifth, you felt bad, and you're asking me what to do? I'm going to tell you, don't do that, and I'm going to get paid for that? And I do.

(Laughter.)

DR. NEILL: So there's a lot about this that's not rational is what I'm suggesting, but that's okay. I'm still getting paid.

With regard to the specific vote, and without saying what my vote is, I'm anxious to hear from others who feel that there is reason within the antacid monograph language for the combination of those indications, given the analgesic/antacid combinations that exist on the market now.

I've not heard a lot of reason for the combination. Since I'm out there, I'll tell you I think aspirin is an amazing wonder drug, and that

is not a matter of opinion but has great data to back it up. It does have some safety issues, but on the balance, there's a reason it's still around. The same is true for many antacids. I'm not sure that sodium bicarbonate is maybe at the top of the list, but it's good still, and it's cheap.

DR. ROUMIE: It's cheap.

DR. NEILL: That's a long way of saying if any of you can advance the thought that there's reason to consider those two together, or the multiple indications within that antacid monograph, I'd be interested to hear it.

DR. ROUMIE: Okay. Dr. Wishingrad?

DR. WISHINGRAD: Just another comment about the rationality question. I think originally, the combination of antacids and caffeine was considered irrational, and it wasn't allowed in the monograph back in the '80s, I guess. But to me, this combination is less rational than that. Antacids and aspirin seems really contradictory to me. One is GI protective, theoretically; one is GI toxic. People have different symptoms, but to combine

these in one product does not seem to be rational.

DR. ROUMIE: Dr. Sanders, do you have another question or comment?

DR. SANDERS: No. Unfortunately, I can't add any illumination to Dr. Neill's question, but I'm trying to go narrow to the definition of the combination rule. And the first is, does each active ingredient make a contribution? That seems reasonable based on the data; the second, when combining, does it not decrease the safety or effectiveness? There seems to be some question about that, insufficient data.

Then the third, that we get to a lot here, is under adequate directions for use and warnings, does it provide a rational concurrent therapy? That's where I think the data is most lacking.

So in terms of guidance to FDA, it seems to be structured that way, and that where it gives me a little bit of a pause. But I would like to hear from perhaps the specialists or internists around the table, if there's additional data that I'm missing.

DR. ROUMIE: Okay. Again to summarize, I think a lot of the same concepts came up, including the combination of the agent and the target population self-selecting and understanding what they are treating.

I think we can go on, and I'm going to read my directions to you all. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed the vote, the vote will be locked in. The vote will be displayed on the screen. The DFO will read the vote from the screen into the record.

Next, we will go around the room, and each individual who voted will state their name and

their vote into the record. You can also state the reasons why you voted as you did, if you want to. We will continue in this same manner until all questions have been answered and discussed.

Let me clarify the voting question. The question is, is the combination of an analgesic with an antacid a rational combination for over-the-counter use for the relief of minor aches, pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea?

(Vote taken.)

DR. ROUMIE: Everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 5 yes, 15 no, zero abstentions.

DR. ROUMIE: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want, you can state the reason why you voted as you did into the record. We can start with Dr. Smith.

DR. SMITH: Tommy Smith. Manchester University. I voted yes. I believe that it met

the minimum threshold of rationality.

DR. ROUMIE: Dr. Aldrich?

DR. ALDRICH: Dawn Aldrich. No.

DR. FARBER: Neil Farber. UC San Diego. I voted no for the reasons that I had previously stated, that I felt there is some risk, including patient misunderstanding, as well as the fact that there are questions about effectiveness.

DR. CHOUDHRY: Niteesh Choudhry. Harvard. I voted yes with the proviso that we're talking about limited use and in the context of overindulgence or hangover, as opposed to unassociated symptoms.

DR. STERGACHIS: Andy Stergachis. I voted no for reasons cited earlier with respect to the use of these combination products for the condition noted.

DR. BESCO: Kelly Besco. I also voted no. Mainly, I believe if these products were used for the short duration that they are prescribed, that they safe and effective. However, my confidence in patients' ability to self-select appropriately and

use them appropriately is somewhat minimal, and that's why I voted no.

DR. WU: Victor Wu. Tennessee Healthcare Finance Administration. I voted no.

DR. PISARIK: Paul Pisarik. I also voted no for the reasons that are mentioned. There are better medications out there, H2 blockers, Maalox. I would never tell a patient who came into my clinic, acid indigestion, take two aspirins and call me in the morning. I mean, I just wouldn't do that.

Somebody also mentioned this, aspirin may cancel out the anti-antacid effect, so they may not be getting any effect from the combination, the sodium load.

In terms of the minor aches and pains, I would see if first treating the heartburn, if that would take care of the minor aches and pains rather than prescribing something on top of the antacid for the minor aches and pains.

DR. SANDERS: Lee Sanders. I voted no for the reasons cited earlier.

DR. BARON: Elma Baron. I voted no.

DR. NEILL: Richard Neill. I voted no.

DR. ROUMIE: Christianne Roumie. I voted no. I think there was a very nice summary by Dr. Sanders about meeting all of the steps in the CFR ruling for combination. And things start to fall apart at the combination being efficacious for each of their separate things, as well as part 3 of that, which is patient understanding.

So I think that's where things really fall down for a lot of people on the panel.

DR. ENGLE: Jan Engle. I voted no for a lot of the reasons I already stated, but also that combination rule states that it should not decrease the safety or effectiveness of any of the individual active ingredients. And I believe that putting aspirin in with the antacids does that.

DR. TYLER: Linda Tyler. University of Utah. I voted no as well. I think when you think about the etiology of the pain here, the minor aches and pains associated with the GI symptoms, again, you don't treat those minor aches and pains

with aspirin. You treat the GI symptoms.

I think some of our frustration is that what we're finding 40-some odd years later is that the monograph system does not keep up with what's happening and is not flexible enough what we're doing. It filled a need at the time, but we get to this point, the four monographs are not coordinated, so that causes some holes and some problems, and they're not contemporary in terms of how we think about managing these disease states. I think that's the other thing I found really challenging in thinking about this.

DR. WARHOLAK: Terri Warholak, and I voted no. In my mind, "rational" means that they don't work at cross-purposes. I think in a lot of ways, they do work at cross-purposes in this combination, so I voted no.

I applaud the FDA for trying to address some of the DESI drugs from way back that are irrational drug products. There's still a lot more out there, just a little plug.

Also, while I'm at it, I really agreed with

Dr. Besco when we were talking about the brand name extensions. I think that's another huge problem that needs to be addressed. I see patients taking things; they don't know what they're taking because it's the brand name, so that should also be looked at in the future.

DR. SOLGA: Steve Solga. I voted yes. I agree -- I applaud the FDA's effort in this regard. It's obviously very challenging to sort through all this.

So many years ago, these medicines separately were considered generally regarded as safe and efficacious, and I've learned nothing this morning to really change that. In the short-term, I don't see the medicines as being irrational, and they certainly are when taken for any length of time.

I think that the FDA's definition of rationality has been met, and I think the public at large would also call this rational.

DR. WISHINGRAD: Marc Wishingrad. I voted no, mostly because of the confusion issue with the

patients.

DR. LIPMAN: Tim Lipman. I voted yes. Although in my heart, I believe no. But I think once you have minor aches and pains, and everything that Dr. Solga said. I think that the product -- the yes was, for me, the appropriate vote.

DR. SCHMID: Chris Schmid. I voted yes. While aware of all the different problems here, I think there's very little evidence that these things cause serious events from the literature we've seen. If they're used properly, they seem to do okay. Most of the problems seem to be with people who were using them against the label.

It does say for the relief of minor aches with these other symptoms. These products do treat both of those causes. I admit that if used improperly, they probably are not good drugs to take, but I don't know that that makes them irrational.

DR. KING: Tonya King. Penn State. I voted no. Along with people being confused by the

labels, I think one of the problems is they don't read them. So that is what it is, but that's something that came to mind.

As a statistician, I don't have the depth of medical training as the clinicians, but I like to think as a statistician, I'm somewhat logical. So as I listened to your discussion, it did not make sense to me to add in an ingredient that would aggravate a symptom that you're trying to treat with the analgesic. That's why I voted no. Sorry. I meant with the antacid.

DR. ROUMIE: Thank you. The last point is a discussion question, and I'll read the question out loud for us.

Hangover is defined in the monograph as a condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic systems 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.

We should discuss whether or not the treatment of hangover is an appropriate indication for over-the-counter drug products. If the hangover indication is appropriate, which ingredients would be options for the treatment of the symptoms?

Dr. Farber? Kick us off.

DR. FARBER: All right. I'll kick us off. I would say no for a number of reasons. First off, all of the products that I've heard about discussed today for hangover indications contained an analgesic. And the two analgesics that we're talking about are either acetaminophen or aspirin, both of which in combination with alcohol can have some serious side effects potentially, especially if used over a long period of time or recurrently.

For that reason, I wouldn't feel comfortable with either analgesic being in the product, and therefore would have to say that that doesn't make sense.

But there's more than that. I have two

other concerns, one of which wasn't really raised a lot today. Basically, there are issues apart from chronic alcoholism that need to be addressed in a binge type of drinking or an overindulgence of alcohol, even if it's singular.

That is that a patient who has a large amount of alcohol is at risk for an episode of acute hepatitis, or acute pancreatitis, or an acute arrhythmia. If the patient, I think, thinks that being able to take something that will relieve their symptoms of a hangover, that therefore they are not at risk for other issues if they do this again, is a risk.

I mean, that worries me. It's not a moral issue. It's not that we want to punish them. I'm an ethicist; I know that's not the case. Rather, the issue is protective, and it's one of beneficence and not maleficence towards that patient.

The third thing is if a patient has some of these side effects after that of drinking, they may be less likely to seek care from their physician,

and therefore an opportunity to discuss binge drinking with that patient if there are over-the-counter agents available.

So for those reasons, I would say no.

DR. ROUMIE: Dr. Neill?

DR. NEILL: It's Richard Neill. University of Pennsylvania. Until Dr. Dr. Rohsenow discussed the distinctions between alcohol intoxication and hangover, I would not have been able to self-diagnose and self-select properly, despite my lengthy experience with both.

This raises for me the question about whether hangover ought to be an OTC indication if consumers can't appropriately self-select. This is tied up in the issue of safety for the reasons that Dr. Farber brings up; there's overlap in these symptoms of headache.

It also occurred to me that symptoms not included in the scales that were used to measure hangover were things like phonophobia, photophobia, and yet they seem incorporated in the term "irritability."

In any event, considering if a consumer can't self-diagnose and self-select, is there a narrow safety window, which if they fall outside, is going to result in a horrible outcome, my sense is that there's not a safety signal currently present despite that inability to self-select.

So I'm struggling a bit because on the one hand, I feel like by the regulatory definition, if we were to objectively measure a consumer's ability to self-diagnose hangover as distinct from, we'd see that it's not very good. If there were actual use studies -- and I would pay to watch that study of the hangover people trying to read and select. But if there were data, which it sounds like there's not for self-selection studies in this instance, I suspect that it would, for all the reasons that have been brought up in terms of cultural differences, health literacy, it would be challenging for consumers to self-select. And still, despite each of those issues, given that these products exist in some form in the market, I've not seen evidence of a safety signal that

leads to concern.

If the discussion is part of the help for the FDA as opposed to the votes that we take earlier, I hope that you hear that if there are implications to the distinction in the OTC indication, it doesn't seem like it meets it, to me. In this instance, it doesn't seem to matter.

DR. ROUMIE: But I would also say that most of the things for over-the-counter would be safety, yes, check. We don't think that this is an unsafe product, but we haven't also seen efficacy.

I would kind of counter with hangover, based on Dr. Rohsenow's data, was a limited event that lasted about three hours. Okay. Show me data that treating this makes you feel better sooner than if I just gave you a big old jug of Gatorade.

DR. NEILL: Richard Neill, again, if I may?

DR. ROUMIE: Yes.

DR. NEILL: From the public health standpoint, because these entities will continue to exist under other names -- Anacin is a combination, I think aspirin and caffeine -- if not the

antacid/analgesic combinations, the fact that the individual components will continue to exist on the shelf and potentially be used suggest to me that, like the other nonregulated supplements and other items, which fail to demonstrate efficacy, at least there's no harm.

In some of individual indications -- I know that when I go and buy acetaminophen, I look for the amount. I'm a single-ingredient bigot; it's true. But that's because I'm not thinking how much more bullet bourbon do I have in my -- plus, I'm also thinking, how bad am I going to hurt after I go out training for my five boroughs bike ride in New York on May the 7th, or if I have another ache or pain, because there are other indications for which there is good evidence of efficacy.

DR. ROUMIE: Dr. Lipman?

DR. LIPMAN: Dr. Lipman. Washington. It seems to me that these -- first of all, I don't understand the definition of hangover anymore. Well, I read in the pre-meeting materials what the FDA has here, and it's very complicated; a very

nice presentation from Dr. Rohsenow, but it seems very self-limited. And I think what the FDA is talking about appears to be hangover, and intoxication, and a broad mix.

I'm not sure if it's me as an individual who's had a binge and then stops drinking. I'm not going to worry at 8 o'clock in the morning, when I'm hopefully trying to get up, whether I'm still intoxicated or have a hangover. I just want to get rid of my headache and my lousy feeling. I think there's a charge to the FDA to define what it is that we're talking about.

Two is, if you take away the combination, well then, I'm reach for my acetaminophen or aspirin because I want something. And, boy, I like the term "Blowfish." I think that's very --

(Laughter.)

DR. LIPMAN: Whoever thought of that term, that name, should be complimented. I mean, if there's a choice between Blowfish and aspirin, I'm going to take Blowfish.

(Laughter.)

DR. ROUMIE: Dr. Smith?

DR. SMITH: I certainly agree with the statements that have been made. Individuals who are experiencing some of these symptoms are going to reach for an analgesic and/or an antacid, either a single -- a monotherapy or a combination therapy.

It's my opinion that a carefully crafted patient-centric label will help individuals use the medication in a safer way. They're going to reach for the aspirin or the Tylenol regardless.

If hangover were listed as an indication, we have an opportunity to educate the patient. We have an opportunity to highlight the risks associated with the use of those drugs. So I think we would be missing that opportunity to help the patient use the drug in a safer way because they're going to use it regardless.

DR. ROUMIE: Dr. Sanders?

DR. SANDERS: This is the fun part of the discussion. There are four concerns that I have. Three, I think, have been addressed pretty well, but the fourth, I just want to highlight and some

people touched on.

One is the natural history, and I think you talked about that earlier, that when you have a condition that's described in the natural history of evolving over the period of 1 to 3 hours, do we really need a new treatment?

The second, which was commented on by the experts already, is the lack of data on efficacy to treat this. The third most important one is the confusion on the definition of hangover.

When I'm sitting around the table of peers and experts in the room who have differing definitions, that's an opportunity for confusion and perhaps an argument against the treatment of hangover as an appropriate indication for OTC products.

The final one is a public health concern. I think this was touched on briefly by other folks, and I think it warrants some discussion. We do have a rising public health concern of alcohol use, and use in concert with other medications, both prescription and non-prescription medications.

Many of the medications that adolescents and young adults that I treat take, alongside alcohol, stimulant medications, pain medications, opiates, and so forth, are themselves contraindications to the use of some of the OTC products being discussed here.

While I agree with my colleague that this might be an opportunity for education of the general public, in general, kids do not go, or young adults, to over-the-counter labels to be educated about this issue.

It is an opportunity for collaboration between FDA with CDC and other agencies around education, but I don't think that the right way to go at it is to create indications for hangover medications that actually might do more harm than good.

DR. ROUMIE: Dr. Engle?

DR. ENGLE: Jan Engle. If these items are going to be allowed to continually be marketed and they have acetaminophen or aspirin in them, one of the things that I think would help is the labeling,

which has been somewhat addressed. But one of the questions we get as pharmacists is a lot of them, I think they say upon wakening, take two tablets or whatever it is.

The problem is that sometimes patients or people with hangovers will say, well, I just went to bed at 4 a.m. and I'm at 6:00 because I got to go to work. Is that long enough? And there's not a lot of guidance on the labeling.

So I think that's something that could be very helpful to consumers, even though I realize not all read the label. But at least to pharmacists and other healthcare professionals, if there was more guidance in how much time should elapse from the last strength to when you take these products, because that's an issue that comes up a lot with consumers in the community setting.

So that's something that, at least if these products are going to be available, maybe we could have better labeling that addresses that point.

DR. ROUMIE: Dr. Solga?

DR. SOLGA: I just wanted to speak for a

moment as a hepatologist about acetaminophen. I'm concerned with the use of acetaminophen, these products, specifically because it's the short-term binge, overnight thing. That's the opposite of what I was saying about aspirin.

As a hepatologist, I don't understand the interaction between acetaminophen and alcohol, and I tried. For the sake of this meeting, I've been back and forth, 533 sites, publications that come up in PubMed when you put in "ethanol and acetaminophen." And the answer is we just don't know. There is not a biologically plausible, well-thought-out mechanism of action for either injury or protective effects.

It's inaccurate to say acetaminophen, bad; alcohol, bad; together, they're worse. That's just not how the liver works. We've been wrong about that over and over again in hepatology.

Too simple but relatively recent examples to the emerging crisis of fatty liver, often associated with obesity, for so many years, we've said, okay, obesity, dietary fat, bad; fatty liver,

bad; don't eat dietary fat. Wrong.

It took many years, but the data, it was just all pointing in the same direction, dietary fat is not not-bad. It's not not-bad. It's protective. It's probably a good thing. Same story when it comes to light alcohol use in the setting of fatty liver; not only not not-bad, but probably good.

What happens to acetaminophen in the background of alcohol use, it's not that you take two bads and you make a worse. You could take two bads and make a better, but I don't know. And I think that in this instance, erring on the side of caution, acetaminophen is a big problem in this setting.

I'd say this as somebody who walks around and sees people who are newly jaundiced all day long in the hospital for a living, and you try to pick through, you know, what happened? What happened last night? Do you remember? And the answer is they often don't. You can only draw so much information out of somebody who's unable to

provide a complete history.

DR. ROUMIE: Dr. Solga, just to clarify for the committee, would you say that alcohol, maybe binge alcohol, and acetaminophen is an unpredictable combination, meaning some patients may be fine and others would not be fine?

DR. SOLGA: Correct. And I feel like the likelihood of harm here is substantial, so I'm more concerned about this than how it came across on others.

DR. ROUMIE: Thank you. Dr. King?

DR. KING: Tonya King. Penn State. In trying to think through this question and realizing that based on the description of the definition of hangover and the symptoms, even though the symptoms might be the same as what you would be trying to treat with an analgesic, the underlying issue is they're caused by alcohol. And if that's already on the warning label for some of these analgesics, then it just doesn't make sense to me why you would include them together.

Even if it's determined that it's okay or

that it should be evaluated further, I think what Dr. Mahowland [sic] said earlier about being able to assess the risk-benefit ratio is really important.

Without having any efficacy data and trying to weigh that against what these concerns could be, I think that that's something -- again, as a statistician, that would be very valuable, to have some efficacy data to see that this is really beneficial.

DR. ROUMIE: Dr. Choudhry?

DR. CHOUDHRY: I think earlier on, Dr. Lipmann and Dr. Neill were talking about the idea that we don't know what a hangover is. I'm not sure that's true. I think most patients know what a hangover is. And whether or not it's at the sort of later phases of intoxication or the earlier phases of blood alcohol level of close to zero -- Dr. Lipman?

DR. LIPMAN: I'm sorry. I don't know what a hangover is. I'm not sure patients know what a hangover is. But what I'm saying is the FDA

definition of a hangover and the presentation definition are different, so that even in the discussion today, we're not clear what a hangover is.

DR. CHOUDHRY: Sure. The definition we were offered before, is kind of where I'm going with this, is the research definition, and it's an appropriate one. We have research definitions for all kinds of things that we use to standardize a study, standardize outcome evaluation, which may be slightly distinct from common usage.

I would argue that common usage of hangover, as somebody who has admittedly generally paternalistic, is well appreciated by most patients who have had one, most individuals who have had one as well.

To the extent that it's a distinct clinical entity that is definable, I would say it is. So the question then becomes, is it an entity that requires treatment or not? That's more debatable. That's perhaps the first point.

Second point, to the extent that we are

going to treat it, so just sort of assuming for a second that it's something that is worthy of treatment or that people desire treatment for, regardless of what we may think for them, the question is what do we treat with?

This is the second part of the discussion question. I'm really compelled by what Dr. Solga has to say and agree with it entirely. From the safety side of the equation, everything we've heard today suggests that aspirin, for a limited use, in short-term settings, as we've now talked about several times, seems okay. Whether or not it's the best idea ever or not, it seems okay.

We have these big questions around acetaminophen and alcohol. So to the extent that we are going to say this is an indication worthy of treatment and we're going to recommend a treatment, my personal position is that an aspirin-containing product seems to be acceptable.

DR. ROUMIE: Dr. Stergachis?

DR. STERGACHIS: That's okay. We're regressing.

(Laughter.)

DR. STERGACHIS: Andy Stergachis. This is a terrific discussion to have before my heading over to the Washington State wine country this weekend.

(Laughter.)

DR. STERGACHIS: Regrettably, we're only presented with two active ingredient products to discuss today, aspirin and acetaminophen, in relation to hangover. I completely agree with what Dr. Solga has indicated, but I want to add one more dimension to the conversation, which is that people get in trouble when they take various products that contain acetaminophen, and they don't know it necessarily.

I was here in the room over at FDA discussing this very issue in relation to the toxicity of acetaminophen, the threshold itself not being so much higher than the -- approximately close to the toxic level and people getting into trouble with liver damage and the like.

I'm jumping ahead to the second part of this. I think acetaminophen should not be one of

the products in the monograph. Even with respect to aspirin or acetylsalicylic acid, unfortunately, the monograph does not take into account how practices have changed relative to taking what may or may not be safer NSAIDs, such as ibuprofen, which I'd like to hear from others, whether or not the monograph process itself allows for taking into account alternative NSAIDs than aspirin alone.

DR. ROUMIE: Dr. Tyler?

DR. STERGACHIS: I wonder if I can get an answer to my question about -- are we limited or restricted to only two products in or out?

DR. ADAH: I'll take the first shot. Steven Adah. The monograph describes products that are eligible for the monograph. It doesn't discuss other products, and it's only a guide meant to get those products to the market. It's not really a prescribing document per se. It is just saying if you want to get these products to market under the monograph, this is how you do it.

If someone wanted to have this indication for ibuprofen or some other product, then they

would do it through the NDA process.

DR. TYLER: Linda Tyler. University of Utah. Thank you. I agree with the concerns about acetaminophen, so again, slightly getting ahead, my background is actually in poison control. And what we don't understand is the dynamics of the toxicity in terms of how the metabolism is affected, especially as you take acetaminophen and then combine it with the alcohol. We don't know the doses; we don't know what tipping point. And our guess would be for every patient, their genetic material also affects all of that.

So I think there's lots of risks and lots of unknowns about acetaminophen in particular that should cause us some concern.

I found it interesting in reading the materials as background, roll it back 40 years ago, it was just assumed these would work for headache. So the idea of what we know about evidence now has never really been applied to the situation.

That being said, the reality is most of us know what a hangover is. Most of us would say

we're going to treat the symptoms. If the headache is the most predominant, we're going to take something for a headache.

I think that's where, in working with consumers, how we label stuff makes a huge difference, and acetaminophen should not contain this labeling. But in the doses and for the acute event, the other agents, aspirin, seem to be relatively safe in that setting.

Likewise, for some of the GI symptoms, other things would be used. But again, we're treating the symptoms; we're not treating the complex, so to speak, and that's the part that we don't really understand well.

I think the doses of caffeine that we're talking about are unlikely to pose any risk and unlikely to pose additional toxicity. Again, thinking that people are going to treat their symptoms, a cup of coffee has more caffeine than the doses that we're talking about here.

DR. ROUMIE: Okay. I'll summarize our discussion. All of the products that we are

talking about in the overindulgence monograph contain an aspirin or an acetaminophen analgesic. There was concern related to those products and the side effects of those products in the setting of alcohol consumption.

There was more concern brought about by the committee related to acetaminophen/alcohol combinations because of its unpredictable dose and side effects on hepatotoxicity.

There was concern related to the ability to self-diagnose and self-select, but given that ability, we did not see any safety signal in the use of these products. To the contrary, we also didn't see any efficacy data that showed that they were more efficacious than placebo or individual treatment.

There was a call for carefully crafted patient label and the opportunities to educate and highlight use of medications if they were to exist for a hangover in a safe and appropriate way.

There was some confusion about hangover definition, which obviously led to these issues of

self-selection. Again, we brought up the issues of combination drugs potentially being a culprit because of patient understanding and the labeling concerns.

There was a concern brought up about labeling that might include something about a time lapse from the last drink to the first dosing of a hangover relief product.

The last thing was Blowfish was a good name.

(Laughter.)

DR. ROUMIE: Overall, I think the committee felt like the aspirin products may be potentially safer certainly from a hepatology standpoint compared to acetaminophen. We had less discussion on aspirin and safety surrounding the gastrointestinal concerns after somebody goes out on a binge drink. Maybe we can hear from our GI colleagues on whether or not there are concerns for that in the setting of an acute binge.

Dr. Wishingrad, and then Dr. Lipman.

DR. WISHINGRAD: A short-term couple of doses of aspirin, I'm not concerned, in the setting

of alcohol binge, as a big risk, just not concerned.

DR. LIPMAN: Agreed, no concern for the short-term.

DR. ROUMIE: Again, this goes back to appropriate labeling on the maximum number of doses in a 24-hour period and then maybe the duration of use, if it were to include an aspirin-containing product.

Dr. Farber?

DR. FARBER: Also, we had discussed some potential public health concerns, one in terms of adolescents, young people.

On the one hand, my concerns about the fact that there are some potential acute effects of binge alcohol that are not well addressed -- not at all addressed in the label and not well addressed in terms of in the public's eye, and that patients may be repeatedly binge drinking like this without knowing what they're in for.

DR. ROUMIE: Thank you. I'll just clarify, with the FDA, if you have the information that you

need from the committee?

DR. FURLONG: I think I've heard what I wanted to hear. Is there anybody in the group that would like to ask any further questions?

(No response.)

DR. FURLONG: Looks good. Thank you.

Adjournment

DR. ROUMIE: Okay. Thank you.

Before we adjourn, are there any last comments from the FDA? I think we heard -- no?

All right. Panel members, the meeting is adjourned. Please take all your personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please remember to drop off your name badge at the registration tables so that they may be recycled.

We will now adjourn the meeting. Thank you.

(Whereupon, at 2:48 p.m., the meeting was adjourned.)