FDA Briefing Document

Joint Nonprescription Drugs Advisory Committee

and

Drug Safety and Risk Management Advisory Committee

Meeting

April 4, 2017

Safety issues associated with over-the-counter analgesic and antacid combination products used for upset stomach and hangover indications

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the safety issues associated with analgesic and antacid combination products used for upset stomach and hangover indications to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Deputy Director for Safety Memorandum

Author: Valerie Pratt, MD

Thank you for your participation in the joint Nonprescription Drugs Advisory Committee (NDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) meeting held on April 4, 2017. As members of the Advisory Committee (AC) you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision making process related to the approval, labeling, and use of drugs for over-the-counter (OTC) marketing in the United States. The upcoming meeting is to discuss safety issues associated with OTC analgesic combination products used for upset stomach (i.e., heartburn, nausea, fullness, belching, gas, acid indigestion, and/or sour stomach) and hangover indications under the Internal Analgesic and Antacid monographs in 21 CFR part 343 and 21 CFR part 331, respectively. Because the indications of upset stomach and hangover are interwoven in these monographs, the committees will also be asked to discuss whether or not the treatment of hangover (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) is an appropriate indication for OTC drug products.

Generally recognized as safe and effective (GRASE) antacid-analgesic combination drug products are currently marketed 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 (i.e., nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability). See Appendix 1 for the list of GRASE active ingredients in the Antacid and Internal Analgesic Monographs. Table 1 below provides a list of indications for these products and the associated monographs under which these indications may be found.

The combination of antacid and aspirin for use in relieving gastrointestinal symptoms has been a point of comment regarding safety throughout the rulemaking process. Because aspirin reduces cytoprotection of the GI mucosa due to dose-dependent impairment of prostaglandin E_2 synthesis and decreases platelet aggregation due to irreversible inhibition of thromboxane A_2 production, bleeding is a known risk with aspirin therapy. However, the Antacid Advisory Panel and the Internal Analgesics Advisory Panel reached different conclusions regarding the safety and labeling of antacid-aspirin combination products. In addressing these concerns, the FDA limited the dosage form of combinations containing aspirin and antacids to oral solutions (since the only safety data available at the time were in reference to that dosage form) and deferred to labeling as the means to ensure proper use of the drug. On the other hand, the OTC monograph allows combinations of antacid and acetaminophen to be either solutions or solid oral dosage forms.

Over the years, revisions to aspirin labeling, such as 21 CFR 201.326 that requires a stomach bleeding warning, have sought to improve the safe use of aspirin in individuals

with a history of stomach complaints. Despite the warning about the risk of serious bleeding added to labeling in 2009, concern for an association between major bleeding events and use of aspirin/antacid products persists due to the widespread availability of these products in retail settings and continued receipt of FDA Adverse Event Reporting System (FAERS) reports of major bleeding events. Accordingly, FDA issued a Drug Safety Communication in June 2016 and is convening this advisory committee to address this concern.

Furthermore, on December 24, 1991, a Tentative Final Monograph (TFM) was published that amended the Antacid and Internal Analgesics monographs to add indications for antacids 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 result of this effort, antacids added the indication "overindulgence in food and drink", the antacid-analgesic combination products added the indications "overindulgence in food and drink" and "hangover" relief, and analgesic-caffeine combination products added the indication "hangover" relief.

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products defined hangover as "a condition consisting of a complex of systems involving the gastrointestinal, neurologic, and metabolic system 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 deemed necessary to demonstrate effectiveness in treating hangover, as the hangover symptom complex is complicated and reflects multiple body disturbances that are manifested by a wide variety of signs and symptoms of varying frequency and severity.

In 2009, the Organ-Specific Warnings FM 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 (NAPQI), the toxic metabolite that causes liver damage. 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.

Although the 1991 Overindulgence TFM ruled out antacid-analgesic-caffeine and antacid-caffeine combination products for the relief of hangover symptoms, it permits the sale of antacid-analgesic combination products for various indications, including "upset stomach associated with hangover". The TFM also proposed the analgesic-caffeine combination drug product for "the 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."

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

Table 1.1 Status of Analgesic/Antacid/Stimulant Combinations (in chronological order)

	Monograph	**Indications for Combination Ingredients**	**Drugs**
		Antacid and Analgesic	**Antacid/Analgesic**
1	Antacid FM (June 4, 1974) 21 CFR 331.15(b)	Antacid: heartburn, sour stomach and/or acid indigestion Analgesic: "concurrent symptoms involved"	GRASE antacid* and GRASE analgesic* marketed in a form intended for ingestion as a solution
2	Antacid FM (August 31, 1982) 21 CFR 331.15(b)	Antacid: heartburn, sour stomach, and/or acid indigestion, and upset stomach associated with these symptoms Analgesic: "concurrent symptoms involved"	GRASE antacid and GRASE analgesic marketed in a form intended for ingestion as a solution
3	Internal Analgesic TFM (November 16, 1988)	For the temporary relief of minor aches and pains with heartburn, sour stomach, or acid indigestion, and upset stomach associated with these symptoms	GRASE antacid and acetaminophen in oral dosage form GRASE antacid and aspirin marketed in a form intended for ingestion as a solution
4	Overindulgence TFM (December 24,	Adds three separate indications	

	1991)		
	4a	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) 1. Establishes the Overindulgence Monograph for overindulgence indications 2. Defines upset stomach due to overindulgence in food and drink symptoms in the Overindulgence Monograph[1] 3. Amends the Antacid Monograph to include the overindulgence indication for antacids alone and in combination with analgesics 4. Amends the Internal Analgesic Monograph for the overindulgence indication in combination with antacids	GRASE antacid and acetaminophen in oral dosage form GRASE antacid and aspirin marketed in a form intended for ingestion as a solution
	Monograph	**Indications for Combination Ingredients**	**Drugs**
		Antacid and Analgesic	**Antacid/Analgesic**
4	4b	For the temporary relief of minor aches and pains with upset stomach associated with hangover 1. Establishes the	GRASE antacid and acetaminophen in oral dosage form

[1] Upset stomach due to overindulgence in food and drink is defined as "a condition which occurs as a result of overindulgence in food and drink and consists of a group of symptoms which includes heartburn, fullness and nausea."

		Overindulgence Monograph for hangover indications 2. Defines hangover in the Overindulgence Monograph[2] 3. Amends the Internal Analgesic Monograph to include the hangover relief indication for analgesics in combination with antacids Antacid Monograph itself is not amended to cross-reference, so this indication is only seen in the Internal Analgesics Monograph (although it applies to both)	GRASE antacid and aspirin marketed in a form intended for ingestion as a solution
	4c	**Stimulant and Analgesic**	**Stimulant/Analgesic**
		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 1. Establishes the Overindulgence Monograph for hangover indications 2. Defines hangover in the Overindulgence Monograph 3. Amends the Internal Analgesic Monograph to include the hangover relief indication for analgesics in combination with stimulants	Caffeine and acetaminophen in oral dosage form Caffeine and aspirin in oral dosage form

[2] Hangover is defined as "a condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic systems that follows recent acute 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."

		(caffeine) 4. Amends the Stimulant Monograph to cross-reference the Internal Analgesic Monograph indication	
	Monograph	**Indications for Combination Ingredients**	**Drugs**
5	Overindulgence TFM (January 5, 2005)	**Antacid and Analgesic**	**Antacid/Analgesic**
		Amends definition of upset stomach due to overindulgence in food and drink to expand associated symptoms[3]	GRASE antacid and acetaminophen in oral dosage form
			GRASE antacid and aspirin marketed in a form intended for ingestion as a solution

Source: Mary Vienna, BSN, MHA

FM = Final monograph; TFM = Tentative final monograph; GRASE = Generally recognized as safe and effective

*See appendix 1 for the list of GRASE antacid and analgesic active ingredients

2 Draft Topics for Advisory Committee Discussion

1. 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.

2. Is the combination of an analgesic with antacids a rational combination for over-the-counter (OTC) 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 proposed monograph as a condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic system that follows recent acute excessive alcohol ingestion. The symptoms may include nausea, heartburn,

[3] Upset stomach due to overindulgence in food and drink is defined as "a condition which occurs as a result of overindulgence in food and drink and consists of a group of symptoms which includes heartburn, nausea, fullness, belching and gas."

thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.

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

   We are particularly interested in a discussion of aspirin or acetaminophen as acceptable ingredients to include in combination products for the treatment of hangover. Consider in your discussion the indications for hangover in the monograph, current labeling for stand-alone aspirin and acetaminophen products, 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.

3.1 OTC Monograph Regulatory Background

Author: Mary Vienna, BSN, MHA

3.1.1 Background

In the United States, analgesic and antacid combination drug products for the relief of gastrointestinal symptoms are regulated as over the counter (OTC) drugs under the OTC drug monograph process. Under this process, premarketing review by the FDA is not required for OTC drug products that meet the standards established in the applicable OTC drug monograph. A monograph is an FDA regulation that serves as a rule book for formulating OTC products by specifying "conditions of use", under which a given category of products is considered to be "generally recognized as safe and effective" (GRASE). These conditions of use identify the active ingredients and their allowed concentrations, and can include other standards such as approved dosage forms, required labeling, and in some cases (such as sunscreens) final formulation efficacy testing. In addition to complying with the terms of an applicable monograph, OTC drugs marketed under this process must also comply with drug registration and listing requirements, current good manufacturing practices, and other applicable labeling requirements.

The OTC drug monograph process was established in response to the 1962 Harris-Kefauver amendments to the Federal Food, Drug and Cosmetic Act, which required drugs to demonstrate efficacy in order to be approved by the FDA. As a result, the FDA was required to evaluate the efficacy of OTC drugs currently on the market, which varied in estimates from 100,000 to half a million drug products. Since FDA review of each product individually was unfeasible, the agency sponsored a study by the National Academy of Science and the National Research Council that examined 420 representative products in a variety of therapeutic categories and concluded that only 25% demonstrated evidence of

efficacy[4]. As a result, in 1972 the FDA initiated the OTC Drug Review, which assigned active ingredients to therapeutic categories, with the intention of establishing a list of safe and effective ingredients for each category. The OTC Drug Review began with the formation of Advisory Review Panels (distinct from the advisory committees of today), comprised of contracted scientists and clinicians that conducted reviews of existing literature and data submitted by industry for the active ingredients listed for a specific therapeutic category. These Advisory Review Panels evaluated the conditions of use for each active ingredient (dosage, indication, population, labeling, etc.) and recommended a list of active ingredients for that therapeutic category that were determined to be safe and effective for FDA's consideration.

The progression from an Advisory Review Panel's recommendations to FDA's establishment of a final OTC monograph requires a multi-step, public rulemaking procedure, with publication in the Federal Register and opportunity for public comment at each step. In general, the process involves publication of the Panel's recommendations in an Advanced Notice of Proposed Rulemaking (ANPR). After consideration of comments and data submitted by the drug industry, medical professionals, scientists, consumers, advocates and the general public, FDA publishes revisions as a proposed rule, also referred to as a Tentative Final Monograph (TFM). After a second round of comment and data evaluation, the FDA publishes a final rule, or Final Monograph, that is also published in the Code of Federal Regulations. OTC products marketed prior to 1972 are allowed to remain on the market until a final rule is issued that establishes an ingredient as not GRASE[5].

3.1.2 Antacid and Analgesic Combination Products in OTC Monographs

Antacid Monograph Rulemaking

The recommendations of the Antacid Advisory Panel were published as an ANPR in the Federal Register on April 5, 1973. The Advisory Panel reviewed antacid active ingredients such as calcium carbonate and magnesium hydroxide (see Appendix 1 for a complete list of GRASE antacid active ingredients); the Panel did not review data regarding other acid reducing agents such as H2 blockers or proton pump inhibitors. The Panel concluded that it was rational to combine an antacid with an analgesic for use by an individual who has concurrent symptoms which require the relief provided by both types of active ingredients. The Panel also concluded that fixed antacid-aspirin combinations were irrational for antacid use alone, citing the risks of aspirin toxicity and the potential for damage to the gastrointestinal mucosa[6]. The FDA published its proposed rule, or TFM, on November 12, 1973, which addressed a number of comments that contended that the combination of aspirin and antacids were unsafe for use in individuals with gastric complaints and that the combination be used exclusively as an analgesic. The FDA agreed that antacid-aspirin

[4] 37 FR, pg 85
[5] 38 FR, pg 8714
[6] 38 FR, pg 8721

combination products should not be used by patients with gastric diseases except on the advice of a physician, but concurred with the Panel's recommendation that there is a significant population for which the combination provides rational concurrent therapy, and concluded that labeling would be sufficient to assure proper use of such products[7]. The final rule, or Antacid Final Monograph, was published on June 4, 1974, and revised the monograph regarding combination antacid-analgesic products in response to public comments. As a result of a number of comments questioning the safety of antacid-aspirin combination products for treatment of gastrointestinal symptoms, the monograph was amended to limit the combination products to those administered in a liquid form, as all safety data available at the time were derived from studies and experience with products in solution. In addition, in response to a comment that stated that combination products should be limited to an antacid and an analgesic other than salicylate, the FDA noted that the safety of analgesic ingredients was currently under review by the Internal Analgesic Panel, and accordingly, the safety, effectiveness and appropriate labeling of the analgesic component remained under review by the Internal Analgesic Panel[8]. The Antacid final monograph thus states at 21 CFR 331.15(b) that an antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g. headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

Internal Analgesic Monograph Rulemaking

The recommendations of the Internal Analgesic Advisory Panel were published in the Federal Register on July 8, 1977[9]. In contrast to the Antacid Advisory Panel, the Internal Analgesic Panel recommended that only nonsalicylate analgesic products be combined with antacid ingredients for the relief of concurrent symptoms, and that aspirin combined with antacid ingredients (regardless of antacid strength) be limited in labeling to the analgesic indications only. The Panel found it irrational to provide claims for an antacid effect, since aspirin may potentiate peptic ulcer, cause stomach distress or heartburn.[10] The Commissioner acknowledged the disparity between the Antacid final monograph and the recommendations of the Internal Analgesic Advisory Panel, and sought comment on the recommendations. The FDA published the Internal Analgesic, Antipyretic, and Antirheumatic Drug Product TFM on November 16, 1988. The TFM established the GRASE doses for aspirin and acetaminophen for adults to be 325-650 mg every 4 hours, 325-500 mg every 3 hours, or 650-1000 mg every 8 hours, not to exceed 4,000 mg in 24 hours. In response to comments for and against the prohibition of an antacid relief claim for aspirin-antacid combination products, the FDA concurred with the Panel's recommendation that aspirin products should not be used by consumers who have ulcers, bleeding problems, or recurring or persistent stomach problems. However the Agency cited a lack of data

[7] 38 FR, pg 31265
[8] 39 FR, pp 19869-19870
[9] 42 FR, pp 35346-35494
[10] 42 FR, pg 35370

showing that highly buffered aspirin[11] for solution presents the risk of massive gastrointestinal hemorrhage or that using these products with alcohol increases such risks in normal individuals, and therefore proposed that antacid-aspirin combination products for solution be GRASE for concurrent symptoms. The FDA did not propose to restrict acetaminophen-antacid products to dosage forms intended for ingestion as a solution, because acetaminophen does not have the adverse effects on the gastrointestinal tract that are associated with aspirin.[12] In the same rule, the FDA concluded that it was necessary to advise consumers who have persistent or recurring stomach problems which may be symptoms of an underlying gastrointestinal disorder against using products containing plain or buffered aspirin unless directed by a doctor. Therefore, the FDA changed the Internal Analgesic Panel's recommended warning "Do not take this product if you have stomach distress", to "Do not take this product if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor."[13] A final rule, or Final Monograph, has not yet been published, so currently the 1988 TFM allows under 343.20(b)(1) acetaminophen to be combined with any antacid ingredient, and under 343.20(b)(3) aspirin to be combined with any antacid ingredient and marketed in a form intended for ingestion as a solution.

See Appendix 1 for the list of GRASE active ingredients in the Antacid and Internal Analgesic Monographs.

3.1.3 Labeling for Antacid-Analgesic Combination Products

The labeling indications for antacids established in the 1974 Antacid Final Monograph are symptom relief for heartburn, sour stomach and/or acid indigestion. On September 21, 1979, a proposed rule was published to amend the final monograph to allow an additional indication of "upset stomach", as a term used by consumers to describe symptoms associated with gastric hyperacidity. A final rule was published on August 31, 1982 that amended the Antacid final monograph indications to state "For the relief of" (optional, any or all of the following) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement "and upset stomach associated with "(optional as appropriate)" this symptom" or "these symptoms".[14] On December 24, 1991, a TFM was published that amended the Antacid and Internal Analgesics monographs to add indications for antacids and antacid-analgesic combination drug products for "upset stomach associated with overindulgence in food and drink" with the associated symptoms of "heartburn, fullness and nausea" and to add the indication "upset stomach associated with hangover" for antacid-analgesic combination drug products. These amendments were part of a larger effort to establish a separate monograph for Overindulgence, which allotted appropriate

[11] For purposes of the rule, the term "highly buffered aspirin" is distinct from buffered aspirin. Highly buffered aspirin contains a sufficient quantity of buffering ingredients to conform to the specifications for antacids established in the final monograph for OTC antacid drug products [21 CFR 331.10].
[12] 53 FR, pg 46227
[13] 53 FR, pg 46220
[14] FR 47, pg 38484 and 21 CFR 331.30(b)

indications related to relief of such symptoms to the related monograph categories. As a result of the Overindulgence monograph effort, antacids added the indication "overindulgence in food and drink", the antacid-analgesic combination products added the indications "overindulgence in food and drink" and "hangover" relief, and analgesic-caffeine combination products added the indication "hangover" relief. A proposed rule was published on January 5, 2005, that amended the Overindulgence TFM to revise the definition of "upset stomach due to overindulgence in food and drink" to consist of a group of symptoms that includes "heartburn, nausea, fullness, belching and gas."[15] No final rule, or Final Monograph, has yet been published, so currently the TFMs adding these indications and symptoms provide for such marketing.

3.1.4 Hangover

OTC products for the relief of hangover symptoms were evaluated by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which also considered drug products for the relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food. The recommendations of this panel were published in the Federal Register on October 1, 1982, which concluded that, while overindulgence in the combination of alcohol and food can be manifested in layman's terms as an "upset stomach" and is sometimes confused with the overlapping symptoms of a hangover due to overindulgence in alcohol alone, symptoms of an upset stomach can occur within one hour of overindulgence and persist for periods up to 24 hours and produce a distinctive syndrome of reproducible complaints that consist primarily of nausea, heartburn and fullness[16]. Hangover is a word commonly used to describe symptoms encountered several hours after the sporadic ingestion of large amounts of alcohol, and a review of the literature by the Panel found approximately 30 symptoms used in describing "hangover". As no study was identified that delineated the frequency of these symptoms in a larger population, the Panel developed a list of the most frequently recurring hangover symptoms mentioned in the literature review. The Panel defined hangover as "a condition consisting of a complex of systems involving the gastrointestinal, neurologic, and metabolic system 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 deemed necessary to demonstrate effectiveness in treating hangover, as the hangover symptom complex is complicated and reflects multiple body disturbances that are manifested by a wide variety of signs and symptoms of varying frequency and severity. Therefore, it would be logical to allow consumers to self-treat hangover symptoms with various combinations of analgesics, antacids and stimulants which have been extensively reviewed by other panels for treating the different symptoms that comprise a hangover[17].

[15] FR 70, pg 745
[16] FR 47, pg 43543
[17] 47 FR, pp 43543 and 43551

On December 24, 1991 the FDA published the TFM for the Overindulgence monograph, in which they proposed the addition of the indications "hangover" for the antacid-analgesic and analgesic-caffeine combination drug products. The agency concluded that the Advisory Panel failed to adequately consider that caffeine stimulates gastric secretion of hydrochloric acid and that the target population considered by the Panel did not specifically include individuals who already had some degree of stomach or gastrointestinal irritation or upset due to overindulgence in alcohol and/or food. The agency stated that combination products that contain caffeine, which stimulates hydrochloric acid secretion, and an antacid, which reduces the concentration of hydrochloric acid and treats symptoms associated with high levels of hydrochloric acid, are irrational.[18] Thus the TFM ruled out antacid-analgesic-caffeine and antacid-caffeine combination products for relief of hangover symptoms, and proposed the antacid-analgesic combination drug product for:

1. the temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion, and upset stomach associated with these symptoms,
2. the temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion, and upset stomach associated with hangover, and/or,
3. the temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion, and upset stomach associated with overindulgence in food and drink.

The TFM also proposed the analgesic-caffeine combination drug product for "the 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."[19] The GRASE dose for caffeine is established in the Stimulant Final Monograph as 100-200 mg not more often than every 3-4 hours.

3.1.5 Summary

Currently, antacid-analgesic combination drug products are marketed 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 (i.e., nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability).

Antacid-acetaminophen combination drug products are not limited in the oral dosage forms that can be marketed. However antacid-aspirin combination drug products are limited to dosage forms intended for ingestion as a solution. The combination of antacid and aspirin for use in relieving gastrointestinal 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 addressing these concerns, the FDA limited the combination dosage form to solution (since the only safety data available at the time were in reference to that dosage form) and deferred to labeling as the means to ensure proper use of the drug.

[18] 56 FR, pg 66746
[19] 56 FR, pg 66764

Over the years, revisions to aspirin labeling have sought to improve safe use of aspirin in individuals with a history of stomach complaints. In addition to the warning in the Internal Analgesic TFM "Do not take this product if you have stomach problems (such as heartburn, upset stomach or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor.", revised warnings regarding alcohol use and stomach bleeding were proposed in the Federal Register on November 14, 1997 and December 26, 2006.[20] A final rule regarding liver and stomach bleeding warnings was published in the Federal Register on April 29, 2009, and is codified at 21 CFR 201.326, which requires aspirin to contain a stomach bleeding warning which states:

Stomach bleeding warning: This product contains a NSAID, which may cause severe stomach 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 nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Additionally, the "**Ask a doctor before use if**" warning was revised to include two bullets regarding stomach bleeding and stomach complaints:

- stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn[21]

Therefore labeling instructions for aspirin instruct a consumer to ask a doctor before use if they have a history of heartburn, a symptom for which the consumer might take an antacid-analgesic combination product.

The FDA overruled recommendations of the Internal Analgesics Advisory Panel when the Internal Analgesic TFM was published in 1988, citing a lack of data showing that highly buffered aspirin for solution presents the risk of gastrointestinal hemorrhage as the rationale for proposing that antacid-aspirin combination products for solution be GRASE for relief of gastrointestinal complaints such as heartburn, sour stomach, acid indigestion, upset stomach with nausea, fullness, belching and gas, and upset stomach associated with hangover. The current advisory committee meeting provides the opportunity to reconsider the issue with more recent data and 28 years of labeling experience and revisions.

3.2 Overview of Postmarketing Experience

Author: Office of Surveillance and Epidemiology

[20] 62 FR, pp 61041-61057 and 71 FR, pp 77314-77352
[21] 74 FR, pp 19408 and 19409

The objective of these analyses was to identify serious adverse events (SAEs) associated with OTC analgesic combination products indicated for hangover or overindulgence (i.e., upset stomach), primarily major bleeding events associated with the aspirin (ASA) or salicylate component and liver toxicity events associated with the acetaminophen component. The Office of Surveillance and Epidemiology (OSE) analyzed five years of drug utilization patterns, four decades of case reports identified in the literature and the FDA Adverse Event Reporting System (FAERS) database, and published safety data related to the use of OTC effervescent aspirin/antacids, effervescent acetaminophen/antacids, and analgesic/caffeine combinations (effervescent and non-effervescent).[22]

Drug utilization analyses indicate total sales of effervescent aspirin/antacid products declined from a peak of approximately 8.8 million packages sold in the 12-month period ending in July 2013 to 8.4 million packages sold in the 12-month period ending in July 2016. There were no sales of effervescent acetaminophen/antacid products captured in this database for the review period. An analysis of analgesic and caffeine combination products based on active ingredient was also performed. However, the majority of combination analgesic/caffeine products captured were for products marketed under other monographs and indications, not the hangover or overindulgence monographs.

FAERS analyses resulted in a total of 20 cases of major bleeding events, defined as a hemorrhage from any site resulting in either hospitalization or a blood transfusion, and effervescent aspirin/antacid products (retrieved from January 1, 1969 - July 31, 2016). Seventy percent of the cases reported concomitant use of either an antithrombotic (n=2) or one or more NSAIDs (n=12). There was one fatal case reported in a patient with a history of gastric ulcers and aspirin use. There are likely more cases that exist, but because of underreporting, variable data quality in FAERS, and our restrictive case definition, our search revealed these few cases only. There were no cases retrieved for analgesic/caffeine combination products indicated for overindulgence/hangover or effervescent acetaminophen/antacid products, which was expected based on lack of sales noted from FDA drug utilization analysis.

No relevant observational studies were identified from the literature search. Literature reviews of the randomized controlled trials (RCTs) concluded that they were generally short-term trials of pain relief and thus were unable to adequately assess the long-term safety of antacid-analgesic combinations or analgesic-caffeine combinations. The trials typically gave participants one or two doses to administer as needed and the follow-up period for symptomatic relief and adverse effects was short: hours to days. As a result, the RCTs were uninformative regarding adverse effects associated with either long-term use or frequent use of these drugs. Even the safety of use for a week-long period could not be reliably evaluated by these RCTs. In addition, the RCTs had relatively small numbers of participants, so their statistical power to detect uncommon adverse events was less than optimal. The numbers of

[22] FDA's tentative final monograph for over-the-counter analgesic drugs specified that all aspirin-antacid combination drug products for internal use approved for treating gastrointestinal upset or hangovers are to be administered via a solution, so that they all are effervescent.

RCT participants treated with effervescent aspirin/antacids or effervescent acetaminophen ranged from 45 to 222 and ranged up to 482 among patients treated with analgesic-caffeine combinations. A recent systematic review of bleeding risk among users of low-dose aspirin estimated incidence rates of 0.48-3.64 gastrointestinal bleeding cases per 1,000 person-years of exposure, indicating that the RCTs studied too few people to be able to identify increased gastrointestinal bleeding risk among analgesic-antacid users (Garcia Rodriguez, Martin-Perez et al. 2016). Gastrointestinal adverse events were among the most common adverse events, but it is unclear whether these mostly minor adverse events are predictive of serious adverse gastrointestinal events. Some, but not all RCTs, reported that the patients allocated to effervescent aspirin/antacids, effervescent acetaminophen/antacids, or analgesic-caffeine combinations (both effervescent and non-effervescent) had increases in gastrointestinal symptoms relative to placebo controls.

Patient-level and/or consumer utilization data were not available for analysis and the findings presented should be interpreted in the context of the known limitations of the database used. While analysis of the sales distribution data based on active ingredients shows that analgesic/antacid and analgesic/caffeine combination products are widely sold from manufacturers to retail pharmacy outlets, the sales distribution data represent a wide range of product indications and do not solely include the sales of products sold for overindulgence or hangover indications. In addition, the sales distribution data shown are likely an underestimation of total availability as the proprietary database utilized in the analysis is estimated to capture approximately 50% of the total OTC market.

Likewise, attempts to conduct a FAERS assessment of liver toxicity with effervescent acetaminophen/antacid products yielded no cases as a commercially available product is not marketed in the United States. Furthermore, analyses of randomized controlled trials of analgesic-antacid or analgesic-caffeine combination drugs are unable to adequately assess the effects of frequent doses or long-term safety risks of these drugs because of the trials' short follow-up periods, infrequent doses, and relatively small sample sizes.

In summary, concern for an association between major bleeding events and use of effervescent aspirin/antacids persists based on evidence of continued widespread availability of these products in retail outlet settings (described below), a lack of clear clinical rationale for the combination of aspirin and antacid in a single product for overindulgence or hangover, and continued receipt, albeit few in number, of FAERS reports of major bleeding events. Major limitations of existing data hamper our ability to provide a meaningful assessment of potential adverse events associated with analgesic/caffeine and effervescent acetaminophen/antacid products, but there is no reason to think that caffeine would block the known adverse effects from aspirin or acetaminophen. Although the risk of bleeding events occurring with analgesic/caffeine combinations exists due to the aspirin or salicylate component, we could not find specific adverse event reports for these products. However, the lack of these reports does not indicate that these products are safe for relief of gastrointestinal symptoms.

3.2.1 Sales Distribution Data

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Data Sources Used

A proprietary drug utilization database available to the Agency was used to conduct this analysis (see **Appendix 2** for a full database description).

Sales Distribution Data

QuintilesIMS's National Sales Perspectives™ database was used to obtain national estimates of sales in the number of packages of effervescent aspirin, effervescent acetaminophen and combination products containing caffeine and acetaminophen or aspirin sold from manufacturers to the various channels of distribution, from August 1, 2011 through July 31, 2016, annually. Of note, IMS estimates their projections of over-the-counter (OTC) products to be approximately 50% of the total OTC market.

Product Search Strategy

Effervescent aspirin products containing aspirin/anhydrous citric acid/sodium bicarbonate and combination analgesic/caffeine products containing acetaminophen/caffeine, aspirin/caffeine or acetaminophen/ aspirin/caffeine were included in this analysis. The ability to search for products by *product indication or directions for use was not available at the time of this review; therefore products which are not intended for use in overindulgence or hangover were also captured in this analysis*.

Drug Utilization Results

Table 3.2.1.1 displays the nationally estimated number of packages for effervescent aspirin/antacid and effervescent acetaminophen/antacid products sold from manufacturers to U.S. retail outlets (e.g. chain pharmacies, food stores and independent retail stores) from August 1, 2011 through July 31, 2016, annually. Total sales of effervescent aspirin/antacid-containing products declined from a peak of approximately 8.8 million packages sold in the 12-month period ending in July 2013, to 8.4 million packages sold in the 12-month period ending in July 2016. There were no sales of effervescent acetaminophen/antacid products captured in the IMS database for the review period.

Table 3.2.1.1 Nationally estimated number of packages[1] sold for effervescent aspirin/antacid and effervescent acetaminophen/antacid products from manufacturers to U.S. retail outlets, August 1, 2011 – July 31, 2016

	Aug 2011-July 2012		Aug 2012-July 2013		Aug 2013-July 2014		Aug 2014-July 2015		Aug 2015-July 2016	
	Packages	*Share*	Packages	*Share*	Packages	*Share*	Packages	*Share*	Packages	*Share*
	N	%	N	%	N	%	N	%	N	%
effervescent aspirin/antacid	**8,408,050**	***100.0%***	**8,838,432**	***100.0%***	**8,695,698**	***100.0%***	**8,658,425**	***100.0%***	**8,391,377**	***100.0%***
ALKA-SELTZER	6,418,350	*76.3%*	6,957,980	*78.7%*	7,054,461	*81.1%*	7,003,761	*80.9%*	6,674,550	*79.5%*
ALKA-SELTZER EX STR	1,478,716	*17.6%*	1,400,678	*15.9%*	1,221,034	*14.0%*	1,213,014	*14.0%*	1,231,967	*14.7%*
PAIN RELIEF	265,619	*3.2%*	214,016	*2.4%*	183,542	*2.1%*	206,661	*2.4%*	299,808	*3.6%*
ASA/SOD BIC/CIT	212,060	*2.5%*	218,688	*2.5%*	194,419	*2.2%*	190,525	*2.2%*	177,964	*2.1%*
EFFERVES ANTACID&PAIN	28,979	*0.3%*	22,799	*0.3%*	27,626	*0.3%*	44,416	*0.5%*	6,891	*0.1%*
EFFERVESCENT PAIN RELIEF	4,326	*0.1%*	24,271	*0.3%*	14,616	*0.2%*	48	*0.0%*	197	*0.0%*
effervescent acetaminophen/antacid	**no data return**									

Source: IMS Health, IMS National Sales Perspectives™. Aug 2011 - Jul 2016. Extracted November 2016. File: NSP 2016-1449 Overindulgence products 11-4-16.xlsx

[1]Packages refers to the number of pill bottles or blister packs sold

***** QuintilesIMS estimates their projections of the total over-the-counter (OTC) market to be approximately 50%.

Table 4.2.1 in **Appendix 2** displays the nationally estimated number of packages sold for combination analgesic/caffeine products from manufacturers to U.S. retail outlets of distribution from August 1, 2011 through July 31, 2016, annually. The total number of packages sold for combination analgesic/caffeine products fluctuated from approximately 21 – 22 million packages sold annually. Of note, the OTC sales data shown in Table 4.2.1 in **Appendix 2** were captured based on active ingredients and not by the indication for use. The majority of combination analgesic/caffeine products captured were found to be products marketed under other monographs and indications, not the hangover or overindulgence monographs.

Drug Utilization Discussion

The drug utilization analysis in this review provides an overview of sales from manufacturers to retail outlets for the products of interest and gives context to the reports identified in the FAERS analysis. Our findings show that effervescent aspirin/antacid and combination analgesic/caffeine products are widely sold from manufacturers to retail pharmacy outlets. However, product sales are based on the number of packages sold by the active ingredient. Therefore, the sales data represent a wide range of product indications and do not solely include the sales of products sold for overindulgence or hangover indications. For example, the OTC sales distribution data indicate that the majority of the products captured containing combination analgesic/caffeine included products with labeling for other indications or intended uses such as to treat pain (relevant to monographs for analgesia or menstrual drug products). In addition, manufacturers may change the formulation or active ingredients for some brand name products during the lifecycle of the product under the monograph. Consumers may not be aware of all changes to the active ingredients of brand name products during the lifecycle of the product.

IMS' sales data represent the amount of product being sold from manufacturers and distribution centers into the "back door" of various drug dispensing outlets such as outpatient retail pharmacies, food stores, hospitals and clinics. It does not reflect what is

being sold directly to consumers. Sales data may be a surrogate for consumer use if we assume consumer and store purchasing behaviors are reflective of actual use. *IMS estimates their projections of OTC products to be approximately 50% of the total OTC market.*

Furthermore, IMS' sales data do not include data from internet sales, convenience stores (e.g. gas stations), specialty stores or vending machines. Patient-level or consumer utilization data were not available for analysis and statistical tests of trend were not conducted for any of the data presented in this review, and our findings should be interpreted in the context of the known limitations of the database used.

3.2.2 Pharmacovigilance Data

Authors: Margee Webster, PharmD, BCPS and Lynda McCulley, PharmD, BCPS, Office of Surveillance and Epidemiology

FDA Adverse Event Reporting System Review

The Division of Nonprescription Drugs Products requested this review from the Office of Surveillance and Epidemiology in preparation of this NDAC meeting, which addresses the safety of OTC analgesic combination products indicated for hangover or overindulgence. The objective of this review is to identify serious adverse events reported to the FDA Adverse Event Reporting System (FAERS) related to: 1) major bleeding with OTC effervescent aspirin/antacid products indicated for overindulgence in food and drink, and analgesic/caffeine products indicated for hangover, and 2) liver toxicity events with effervescent acetaminophen/antacid combinations indicated for overindulgence in food and drink.

The findings of this review assess safety issues including the appropriateness of indications for treatment of gastrointestinal symptoms on labels for effervescent aspirin/antacid products, which are known to cause gastrointestinal bleeding; and the concern that effervescent acetaminophen/ antacid products may be harmful if used for the treatment of hangovers due to liver toxicity of both acetaminophen and alcohol.

Since there are no currently marketed effervescent acetaminophen/antacid products available on the US market, we did not investigate liver injury associated with effervescent acetaminophen/antacid products further.

Case Definition for Major Bleeding

Since an objective of this review included an in-depth evaluation of serious adverse events related to major bleeding associated with OTC analgesic (e.g., aspirin, salicylate) combination products indicated for overindulgence or hangover,

Cases were included if:

- The major bleeding event resulted in hospitalization or blood transfusion
  AND
- The case reported a temporal association with an OTC combination product with aspirin or salicylate indicated for overindulgence or hangover.

Cases were excluded if:

- The bleeding event did not result in hospitalization or blood transfusion
- The case did not report that a bleeding event had occurred
- The case contained insufficient information to determine the severity of the bleed or determine a temporal association with the product

- The case failed to identify a patient
- The product reportedly used in the narrative did not contain aspirin or salicylate

FAERS Results for Major Bleeding Associated with Analgesic/Caffeine Products (n=0)

The FAERS database was searched from January 1, 1969 through July 31, 2016, for all analgesic/caffeine combination products regulated by a monograph and indicated for hangover relief. No serious adverse events cases were identified for those analgesic/caffeine products (all contain aspirin/caffeine) marketed for the indication of hangover (Blowfish, First Aid Shot Therapy for Hangover Relief, or Bayer AM Extra Strength).

FAERS Results for Major Bleeding Associated with Effervescent Aspirin/Antacid Products (n=20)

The FAERS database was searched from January 1, 1969 through July 31, 2016, for all aspirin/antacid combination products regulated by a monograph and indicated for overindulgence. After applying MedDRA search terms (Version 19.0) for *Hemorrhages* SMQ and the case definition, we identified cumulatively, 20 cases of major bleeding and products containing an effervescent aspirin/antacid combination for the indication of overindulgence. Nineteen of these 20 cases are mentioned in the 41 cases of major bleeding events cited in the June 2016 FDA Drug Safety Communication. Whereas the 20 patients in this review used *only* aspirin containing antacid products for overindulgence, the patients mentioned in the 2016 DSC used a specific brand of antacid for overindulgence, *regardless* of aspirin content.

Table 3.2.2.1 describes the characteristics of the 20 FAERS cases of major bleeding reported with effervescent aspirin/antacid products for this case series. **Appendix 3,** Table 4.3.1 provides a line listing with the FAERS case numbers, FAERS version numbers, and Manufacturer Control Numbers for the 20 cases in this case series.

Table 3.2.2.1: Descriptive characteristics of serious adverse events related to major bleeding reported with effervescent aspirin/antacid products$^{\infty}$ received by FDA from January 1, 1969 † to July 31, 2016 (n=20)

Age (n=16)	Mean Median Range	61 67 24-91
Sex	Male Female Unknown	6 13 1
Initial FDA received date	1970 1973 1996 2000 2002 2003 2004 2005 2006	1 2 1 1 1 1 1 1 1

Table 3.2.2.1: Descriptive characteristics of serious adverse events related to major bleeding reported with effervescent aspirin/antacid products∞ received by FDA from January 1, 1969 ┼ to July 31, 2016 (n=20)		
	2007 2008 2010 2011 2013 2014	1 1 3 2 1 2
Country of reporter	United States Foreign	18 2
Report type	Expedited Direct Periodic	13 6 1
Serious Outcomes*	Death Life-threatening Hospitalized Other serious	1 0 16 8
Reporter	Healthcare Professional Consumer Other Not reported	9 1 3 7
Indication	Gastrointestinal issues Cold/infection Pain (headache) Hayfever Unknown	8 2 1 1 8
Co-suspect medications in addition to effervescent aspirin/antacid€ (n=12)	Aspirin Ibuprofen Naproxen Clopidogrel Indomethacin Prednisone Warfarin	8 4 2 1 1 1 1
Location of major bleeding event	Upper GI Bleed ‡ Lower GI Bleed § Unspecified	10 3 7
Transfusion required?	Yes No Not reported	9 6 5

∞ Alka-Seltzer products containing aspirin were the primary suspect drugs in all of the cases citing major bleeding events.

┼ Adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events as reported by the reporter. A case may have one or more outcomes. All case narratives indicated the patients were hospitalized even if the reporter did not indicate hospitalization as an outcome.

* Search of the entire database

€ More than one agent was used by multiple patients

‡ Upper GI bleed: duodenal ulcer (n=2), hematemesis/melena (n=2), gastric ulcer (n=2), gastrointestinal hemorrhage (n=1), gastric polyps (n=1), Mallory-Weiss Syndrome/hematemesis (n=1), hematemesis/duodenal ulcer (n=1). <u>One report may have multiple locations of GI bleed.</u>

§ Lower GI bleed: rectal hemorrhage (n=3)

The cases reported no dosing details (12), routine use ranging from once a day to "multiple times a day" (5), use as needed (1), and inappropriate use (1).

For cases that reported a time to onset of the major bleeding event (n=8), time to onset ranged from same day to six months and median was nine days. For cases that reported the duration of use of the effervescent aspirin/antacids products (n=9), use ranged from one day to several years and the median was five days. Seventy percent of the cases reported concomitant use of either an antithrombotic (n=2) or one or more NSAIDs (n=12). Additional confounding factors were also reported in the case series. One case reported the patient had a history of alcohol abuse. Another reported a patient with history of GI hemorrhage, melena, antral ulcer, diverticulitis, GI polyps, Barrett's esophagus, increased international normalized ratio (INR) and increased prothrombin time (PT) and myeloproliferative disease with polycythemia. An additional case reported a patient who experienced 2.6 pints of blood loss during prostate surgery which required transfusion. This patient discontinued the effervescent aspirin/antacid product four days prior to surgery (took 2 tablets a day for 5 days). In one case, the patient had a colonoscopy three days prior to experiencing a rectal hemorrhage.

One major bleeding case reported a fatal outcome. The case contained few details and is summarized below.

Fatal Case (n=1)
FAERS case #4248197, 1970, domestic
A 69-year-old female developed a "massive" GI bleed and was hospitalized. The patient had been using aspirin (unknown dose, frequency, and duration of use) plus the effervescent aspirin/antacid product (unknown dose, frequency, duration of use, and indication). The patient had an initial hemoglobin of 8 (no units or normal range reported) which decreased to 5.3 (no units or normal range), and received multiple blood transfusions ("14 units"). The patient was treated with an ice water irrigation of her stomach. The patient died on the fifth day of her hospitalization. No cause of death was provided, and no autopsy was performed. No medical history was provided.

Reviewer's comment: This case did not provide many details and does not provide a complete picture of why or how the patient was using the aspirin/antacid product, if the patient had a history of GI ulcers or other complications, or what caused the GI bleed. The patient's use of an additional aspirin product may have also contributed to the GI bleed.

FAERS Discussion

Cumulatively, the FAERS analysis identified 20 cases of serious adverse events related to major bleeding and the use of effervescent aspirin/antacid products indicated for overindulgence, between January 1, 1969 and July 31, 2016. There were no cases retrieved for analgesic (aspirin)/caffeine products indicated for hangover or effervescent acetaminophen/antacid products indicated for overindulgence due to lack of product availability.

There are likely more cases that exist, but because of underreporting, variable data quality in FAERS, and our restrictive case definition, our search revealed these few cases only. Of note, requirements for reporting of serious adverse events associated with nonprescription drugs to the FDA was not enacted until December 22, 2006 (Public Law 109-462); thus events that occurred in the decades prior to the enactment of this amendment to the Federal Food, Drug, and Cosmetic act may not have been received by FDA. Although the overall number of cases associated with effervescent aspirin/antacid products is unsubstantial relative to the sales/distribution and years these products have been available on the US market, we consider the serious nature of cases resulting in death (n=1), hospitalization (n=16) and blood transfusion (n=9), noteworthy and clinically significant.

The majority of patients using effervescent aspirin/antacid products appeared to have underlying conditions that put them at risk for developing major bleeding, particularly GI bleeding events. At least one risk factor for developing a stomach bleed was reported in 80% (16/20) of patients and included: age > 60 years old (n= 12); concomitant use of antithrombotics (n=2) or NSAIDs (n=12); history of stomach ulcers (n=1); history of alcohol abuse (n=1). In addition, 40% (8/20) of cases reported using effervescent aspirin/antacid products for a GI issue (e.g., heartburn, indigestion, GI pain), which the patients might not have recognized as symptoms of a serious underlying GI condition. Nineteen of the 20 patients ultimately recovered from the event. The death case provided limited details of the patient's underlying medical condition and was confounded by concomitant use of an aspirin product.

Effervescent aspirin/antacid products were the primary suspect drugs in all of the cases citing major bleeding, and the aspirin contained in these products is reasonably likely to have been a contributing factor to these events. The risk of developing a major bleeding event may be due to a number of factors when using an effervescent aspirin/antacid combination product. These risk factors are currently listed in the NSAIDS Drug Facts Label stomach bleeding warning, which states:

"Stomach bleeding warning: This product contains an NSAID which may cause stomach bleeding. The chance is higher if you:
● are age 60 or older
● have had stomach ulcers or bleeding problems
● take a blood thinner (anticoagulant) or steroid drug
● take other drugs containing prescription or nonprescription NSAIDS (aspirin, ibuprofen, naproxen, or others)
● have 3 or more alcoholic drinks every day while using this product
● take more or for a longer time than directed"

The Organ-Specific Warnings Final Monograph for NSAIDS was not published until 2009. Despite the addition of the new stomach bleeding warning to the drug facts label in 2009, we received eight FAERS case reports of serious adverse events related to major bleeding occurring in patients using effervescent aspirin/antacid products thereafter.

Although the FAERS search retrieved few foreign cases (n=2), international regulators have taken action against manufacturers of effervescent aspirin/antacids products by prohibiting gastric indications (Beigel, Matetzky et al. 2007). In addition, the Spanish Agency for Medicines and Medical Devices requested withdrawal of aspirin from an effervescent aspirin/antacid product in 2004 following a negative product safety review (de Abajo, Garcia Rodriguez, et al. 2009). Most recently, the Medicines and Health Products Regulatory Agency of the United Kingdom reviewed the safety of effervescent aspirin/antacid products and also asked the marketing authorization holder to remove the indications related to upset stomach. This action was completed in 2010.

3.2.3 Pharmacoepidemiology Literature and Data

Author: Elisa Braver, PhD, Office of Surveillance and Epidemiology

Pharmacoepidemiology Results

The Division of Epidemiology (DEPI) originally was consulted to determine whether there were relevant observational data on aspirin-antacid and acetaminophen-antacid combination drug products. DEPI's literature searches identified only one observational study focusing on the risks of drugs containing sodium, including effervescent aspirin-sodium bicarbonate combination products (George, Majeed, et al. 2013). That study did not present specific analyses for either effervescent aspirin/antacids or effervescent acetaminophen/antacid drugs, so it was not eligible for this review. The safety data from the randomized controlled trials (RCTs) of effervescent aspirin/antacids or effervescent acetaminophen/antacids are the primary focus of the epidemiologic component of this review. Subsequently, DEPI expanded the search to include drugs that combine analgesics and caffeine, per a request from DNDP.

The 10 RCTs on effervescent aspirin/antacids (7 trials) or effervescent acetaminophen/antacids (3 trials) that were identified from the literature search all were double-blinded (Diener, Busson, et al. 2004; Diener, Eikermann, et al. 2004; Lange, Schwarz, et al. 2000; Langermark and Olesen, 1987; Eccles, Loose, et al. 2003; Reiff, White, et al. 1988; Tfelt-Hansen and Olesen, 1984; Burnett, Schachtel, et al. 2006; Moller, Norholt, et al. 2000; Nystrom, Gustafsson, et al. 1988) and three were double-blinded crossover studies (Diener, Bussone, et al. 2004; Langemark and Olesen, 1987; Tfelt-Hansen and Olesen, 1984). The primary aim of the RCTs was to assess pain relief, but safety data also were collected. In the RCTs, patients suffering from migraine headaches, tension headaches, sore throats, or postsurgical dental pain were randomized to one or more treatment groups, including effervescent aspirin/antacids, effervescent acetaminophen/antacids, non-effervescent aspirin, sumatriptan, ibuprofen, or placebos. Every RCT used effervescent placebos to mimic the appearance of effervescent analgesics.[23] None of the studies focused on treatment of hangover or gastrointestinal symptoms. Most of

[23] One study by Burnett et al. (2006) did not specify whether an effervescent placebo was used; the paper mentioned a "matching placebo."

the trials involved self-administered medication and the keeping of diaries to record symptomatic relief and adverse effects. All but one of the RCTs was sponsored by the manufacturers of effervescent aspirin/antacids or effervescent acetaminophen/antacid drugs. Two of the RCTs were done in the USA and the remaining eight were done in Europe. The numbers of patients studied in each trial ranged from 47 to 433.

The scientific literature on the safety of analgesic-caffeine combination drug products was searched for relevant studies. Three meta-analyses of RCTs and four RCTs were identified for review. RCTs that were included in the meta-analyses were not reviewed separately except for one by Diener et al. (Diener, Pfaffenrath, et al. 2005) and one by Lipton et al.(Lipton, Stewart, et al. 1998) that had detailed information on adverse effects. Studies focusing on medication-overuse headaches were excluded because those did not fall within the scope of this review and such headaches had been reviewed by DEPI and DPV earlier in 2016. All of the reviewed studies were done in Europe. Adverse events largely were reported by patients rather than directly observed; however, one RCT examined the esophagus, stomach, and duodenum via upper endoscopy at baseline and after multiple doses of drug treatment. Details about each of the studies that were reviewed are found in **Appendix 4** Tables 4.4.1 (effervescent aspirin/antacids), 4.4.2 (effervescent or non-effervescent analgesic-caffeine combinations), and 4.4.3 (effervescent acetaminophen/antacids).

Aspirin and Antacid Combination Drugs

A total of seven RCTs (Diener, Busson, et al. 2004; Diener, Eikermann, et al. 2004; Lange, Schwarz, et al. 2000; Langermark and Olesen, 1987; Eccles, Loose, et al. 2003; Reiff, White, et al. 1988; Tfelt-Hansen and Olesen, 1984) and one meta-analysis (Lampl, Voelker, et al. 2007) of three of the seven RCTs investigated effervescent aspirin/antacid drugs compared with placebos or other treatments for pain. The one study done in the USA failed to report information on adverse events, (Reiff, White, et al. 1988) so only six RCTs provided relevant safety data.

All six RCTs had short follow-up periods in which patients were followed over a period of hours during one to four pain episodes (Diener, Busson, et al. 2004; Diener, Eikermann, et al. 2004; Langermark and Olesen, 1987; Eccles, Loose, et al. 2003; Reiff, White, et al. 1988; Tfelt-Hansen and Olesen, 1984). The doses were infrequent, typically a single dose per pain episode, although migraine patients were permitted a second dose during a migraine attack. Four of the six trials excluded patients after randomizations who either were not compliant with treatment or with filling out their symptom diaries, so that the RCT analyses were not purely by intention-to-treat. The major safety findings of the meta-analysis and RCTs are summarized below.

<u>Meta-analysis</u> (Lampl, Voelker, et al. 2007)

- The meta-analysis included three of the four largest RCTs and reported that the percentages of patients with any adverse events were 12% in the effervescent

aspirin/antacids group, 16.2% in the sumatriptan group, and 7.1% in the placebo group.
- Gastrointestinal adverse events occurred in 3.6% of the effervescent aspirin/antacids group, 7.2% of the sumatriptan group, and 2.9% of the placebo group.
- Gastrointestinal events included nausea, vomiting, heartburn, and abdominal pain.

RCTs

- Only one serious adverse event, renal colic, was reported in a participant receiving effervescent aspirin/antacids.
- Compared with placebo patients, the percentages of patients treated with effervescent aspirin/antacids who had adverse events were:
    - Larger (three RCTs) by a few percentage points; (Lange, Schwarz et al. 2000, Diener, Bussone et al. 2004, Diener, Eikermann et al. 2004)
    - Equivalent (two RCTs); (Langemark and Olesen 1987, Eccles, Loose et al. 2003)
    - Lower (one RCT, 8% vs. 12% placebo).(Tfelt-Hansen and Olesen 1984)
- Gastrointestinal event findings were inconsistent among the RCTs. Compared with placebo or other drugs, patients treated with effervescent aspirin/antacids had a somewhat higher percentage of gastrointestinal events in two RCTs, a lower percentage in one RCT, equivalent percentages in one RCT, and missing data in two RCTs.

Acetaminophen and Antacid Combination Drugs

Three RCTs were identified that compared effervescent acetaminophen/antacid drugs with placebos. (Burnett, Schachtel, et al. 2006; Moller, Norholt, et al. 2000; Nystrom, Gustafsson, et al. 1988)

All three RCTs had short follow-up periods in which patients were followed from six hours to one week. Two of the RCTs were for treatment of postsurgical dental pain and one was for treatment of sore throat pain. Doses were either single use or two doses. The major safety findings of the three RCTs are summarized below.

- No serious adverse events were observed.
- In one RCT, 11% of the effervescent acetaminophen/antacids group had any adverse events compared with 5% of the placebo group. (Burnett, Schachtel, et al. 2006) No differences in percentages of patients with adverse events were observed between the effervescent acetaminophen/antacids and placebo groups in the other two RCTs. (Moller, Norholt, et al. 2000; Nystrom, Gustafsson, et al. 1988)
- Some of the adverse events clearly were related to the surgical dental procedures rather than to the drugs.
- Postoperative bleeding occurred more often among patients receiving effervescent placebo (6/62) than among patients receiving effervescent acetaminophen (1/60) in one RCT. (Moller, Norholt, et al. 2000)

Analgesics and Caffeine Combination Drugs

Seven studies were identified and reviewed, including three meta-analyses of RCTs (Derry, Derry et al. 2014; Derry, Wiffen, et al. 2015; Moore, Derry, et al. 2015) and four RCTs (Diener, Pfaffenrath, et al. 2005; Lipton, Stewart, et al. 1998; Dammann, Saleki, et al. 2004; Pini, Guerzoni, et al. 2012). All seven studies involved research with short drug use periods rather than extended use. The studies included ibuprofen-caffeine combinations in addition to combinations of aspirin, acetaminophen, and caffeine in a single drug. Safety was a secondary objective of the studies because the primary objectives of the studies were determining the efficacy of analgesic-combination drugs in treating acute pain from dental surgery, post-episiotomy procedures, and headaches. None of the studies focused on treatment of hangover or gastrointestinal symptoms. Important safety findings are summarized below.

- Serious adverse events were rare.
- In the RCT where upper endoscopies were done on healthy subjects at baseline and after 10 doses of treatment, gastric mucosal erosions and bleeding were rare events, but were more common among subjects receiving aspirin-caffeine combination drugs compared with effervescent aspirin/antacids.
- Compared with placebo, analgesic-caffeine combinations were associated with higher percentages of patients reporting adverse events. Compared with sumatriptan, analgesic-caffeine combinations were less likely to be associated with adverse events.
- Risk ratio (RR) for people with an adverse event taking 200 mg ibuprofen/100 mg caffeine combination vs. placebo was 1.86 (95% CI: 0.91-3.79).
- RR for 100 mg ibuprofen/100 mg caffeine combination vs. placebo was 1.80 (95% CI: 0.83-3.90).
- Gastrointestinal symptoms were the most common adverse event in two of the RCTs that reported detailed information on adverse events, but not in the other RCT.

Pharmacoepidemiology Discussion

No observational studies of aspirin-antacid, acetaminophen-antacid, or aspirin-caffeine products were identified from the literature search. All the identified RCTs were short-term trials of pain relief and thus were unable to adequately assess the long-term safety or effects of frequent doses of antacid-analgesic combinations or analgesic-caffeine combinations. The trials typically gave participants one or two doses to administer as needed and the follow-up period for symptomatic relief and adverse effects was short: hours to days. As a result, the RCTs were uninformative regarding adverse effects associated with either long-term use or frequent use of these drugs. Even the safety of use for a week-long period could not be reliably evaluated by these RCTs.

The RCTs had relatively small numbers of participants, so their statistical power to detect uncommon adverse events was less than optimal. The numbers of RCT participants treated with effervescent aspirin/antacids or effervescent acetaminophen/antacids ranged from 45 to 222 and ranged up to 482 among patients treated with analgesic-caffeine combinations. A recent systematic review of bleeding risk among users of low-dose aspirin estimated incidence rates of 0.48-3.64 gastrointestinal bleeding cases per 1,000 person-years of exposure, indicating that the RCTs studied too few people to be able to identify increased gastrointestinal bleeding risk among analgesic-antacid users (Garcia Rodriguez, Martin-Perez, et al. 2016). These doses are lower than the maximum labeled doses, but bleeding events would also be rare at higher doses.

Gastrointestinal adverse events were among the most common adverse events, but it is unclear whether these mostly minor events are predictive of serious adverse gastrointestinal events. Some, but not all RCTs, reported that the patients allocated to effervescent aspirin/antacids, effervescent acetaminophen/antacids, or analgesic-caffeine combinations (both effervescent and non-effervescent) had increases in gastrointestinal symptoms relative to placebo controls. Commonly reported adverse effects included nausea, vomiting, and heartburn, some of which may have been related to migraine headaches for which the trial participants were taking pain relievers. Whether minor gastrointestinal symptoms are risk factors for serious gastrointestinal events is unknown. The RCT involving healthy volunteers who were administered aspirin or aspirin/acetaminophen/caffeine combinations suggested that mucosal erosions and gastrointestinal microbleeding could occur after several days of exposure (Dammann, Saleki, et al. 2004). Another consideration is that patients with a history of peptic ulcers or gastrointestinal bleeding or vomiting during migraine headaches were excluded from some trials, so this may have lowered the likelihood of serious adverse gastrointestinal events.

Strengths of the RCTs of effervescent aspirin/antacids and effervescent acetaminophen/antacids included use of effervescent placebos to permit fuller estimation of the placebo effect as well as the use of diaries to improve recall of adverse effects. Participants in a clinical trial may unblind themselves if the placebo drugs look different from the study drugs. Diaries can improve recall of adverse events, but are not necessarily filled out accurately and completely by all participants.

Several RCTs excluded patients randomly assigned to treatment groups who were not fully compliant with the trial procedures, so these trials did not have a pure intention-to-treat analysis. The exclusion of noncompliant patients may lead to imbalances in potential confounding factors between treatment groups, which can result in biased findings. The direction of the potential bias could not be determined.

The best sources of data on serious adverse events from analgesic-antacid or analgesic-caffeine combination drugs are case reports and large studies with long-term follow-up that examined aspirin or acetaminophen as single active pharmaceutical ingredients. There are no RCTs with adequate follow-up time or dosing to assess long-term adverse effects from the combination drug products under consideration in this review. Nor are there

observational epidemiologic studies on analgesic-antacid or analgesic-caffeine combinations that could indicate the risks for either gastrointestinal bleeding or hepatotoxicity. The adverse effects of aspirin and acetaminophen are well-recognized. No observational studies were identified that could indicate whether the known adverse effects from aspirin or acetaminophen are lessened by combining them with sodium bicarbonate or caffeine. As a result, case reports of adverse effects from these specific combination drugs should be combined with existing knowledge on adverse effects from aspirin and acetaminophen as individual active pharmaceutical ingredients to assess safety risks from combination analgesic-antacid or analgesic-caffeine drugs.

3.2.4 Postmarketing Conclusion

Concern for an association between major bleeding events and use of effervescent aspirin/antacids persists based on evidence of continued widespread availability of these products in retail settings and continued receipt of FAERS reports of major bleeding events, despite warning additions to the Drug Facts Labeling for NSAIDS regarding risk of bleeding events. Major limitations of existing data hamper our ability to provide a meaningful assessment of potential adverse events associated with analgesic/caffeine and effervescent acetaminophen/antacid products, but there is no known reason to think that caffeine would block the known adverse effects from aspirin or acetaminophen. Although the risk of bleeding events occurring with analgesic/caffeine combinations exists due to the aspirin or salicylate component, we could not find specific adverse event reports for these products. However, the lack of these reports does not indicate that these products are safe for relief of gastrointestinal symptoms.

While sales distribution data show that analgesic/caffeine combinations are widely sold from manufacturers to retail pharmacy outlets, the sales data represent a wide range of product indications and do not solely include the sales of products sold for overindulgence or hangover indications. Likewise, attempts to conduct a FAERS assessment of liver toxicity with effervescent acetaminophen/antacid products proved futile due to lack of evidence of product availability, confirmed by lack of domestic sales. Furthermore, analyses of randomized controlled trials of combination analgesic-antacid or analgesic-caffeine combination drugs are unable to adequately assess the effects of frequent doses or long-term safety risks of these drugs because of their short follow-up periods, infrequent doses, and relatively small sample sizes.

3.2.5 Postmarketing References

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3.3 Clinical Perspective

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3.3.1 Introduction

This meeting of the Nonprescription Drug Advisory Committee (NDAC) and Drugs Safety and Risk Management (DSaRM) Advisory Committee will address the safety of OTC analgesic-antacid and analgesic-stimulant combination products. There are four monographs that permit the sale of these products. As written in these monographs, analgesic-antacid combination drug product(s) are indicated for symptomatic treatment of overindulgence due to food or drink and hangover, and analgesic-stimulant combination drug products are indicated for the relief of symptoms from hangover. Combinations of antacids with aspirin (ASA), acetaminophen, and caffeine are permitted.

The Division of Nonprescription Drug Products (DNDP) is concerned that aspirin-antacid products are not an appropriate combination for the treatment of heartburn and gastric symptoms from overindulgence due to food and drink. This review will outline clinical safety concerns of analgesic-antacid combination drug products, in particular, aspirin combined with an antacid which may be used to treat gastrointestinal symptoms associated with minor aches and pains. Bleeding is a known risk associated with aspirin therapy. Aspirin is known to reduce cytoprotection of the gastrointestinal tract due to its dose-dependent impairment of prostaglandin E_2 synthesis, and it decreases platelet aggregation due to irreversible (unlike other NSAIDs) inhibition of thromboxane A_2 production (Beigel, Matetzky, et al. 2007). In some cases, consumers seeking these products for relief of heartburn-type symptoms may have an undiagnosed gastric illness for which aspirin use is contraindicated. Such consumers may unknowingly place themselves at greater risk for gastric bleeding by using an aspirin-antacid combination drug products rather than one containing an antacid alone.

The analgesic-caffeine combination products are indicated for the temporary relief of gastric symptoms from overindulgence in food and drink or a hangover. As noted above, bleeding is a known risk associated with aspirin therapy. Acute and chronic consumption of alcohol can cause esophageal and gastric inflammation and increase the symptoms of heartburn (Rocco, Compare, et al. 2014). In addition, alcohol has significant effects on the liver through multiple chemical pathways, including changes in the cytochrome P450 CYP2E1 activity level and an increase in inflammatory cytokines which may lead to alcoholic liver disease including cirrhosis of the liver. Acetaminophen is the drug most frequently associated with drug-induced hepatotoxicity in the United States (Ghanem, Perez, et al. 2016). In clinical situations involving acute or chronic overuse of acetaminophen, a toxic intermediary, N-acetyl-p-benzoquinone imine (NAPQI) is produced in the liver. In certain situations, alcohol and acetaminophen may compete for glutathione which is necessary to detoxify/metabolize both of these substances. Deficiency in glutathione levels may lead to increased risk of liver toxicity (Court, Duan, et al. 2001; Muldrew, James, et al. 2002). For these reasons, acetaminophen-caffeine combination products may not be appropriate to treat symptoms of overindulgence from food and drink and the symptoms of hangover due to acetaminophen and alcohol's deleterious effect on the liver.

The purpose of this review is to outline the clinical safety of these combination products and whether it is rational to allow these combination products as part of the monograph.

3.3.2 Regulatory Background

3.3.2.1 Food and Drug Administration Actions

During the over-the-counter (OTC) Drug Review in the 1970's, the Advisory Panel for Internal Analgesic, Antipyretic, and Anti-rheumatic (IAAA) drug products concluded that fixed aspirin-antacid combination products are irrational for antacid use alone and recommended that it not be labeled or marketed for such use (38 Federal Register (FR) 8714 at 8721; April 5, 1973). This recommendation was reviewed by the FDA Commissioner in 1973. The FDA Commissioner recognized that there may be a theoretical safety concern with the use of aspirin in combination with an antacid for gastric indications. However, the FDA Commissioner noted that the available data at that time showed some benefit to this combination and there were no available studies indicating such a combination was unsafe. The FDA Commissioner stated this issue would be reconsidered if additional data were provided to show that the aspirin-antacid combination caused gastrointestinal (GI) hemorrhage and that the proposed labeling was sufficient to protect the public (38 FR 31260 at 31265).

Thus, Antacid Products for OTC Human Use monograph was finalized on June 4, 1974 (39 FR 19862) for the treatment of 'heartburn", "sour stomach", and "acid indigestion". Numerous active ingredients were approved which include:

- Aluminum-containing active ingredients
- Bicarbonate-containing active ingredients
- Bismuth-containing active ingredients
- Calcium-containing active ingredients
- Citrate-containing active ingredients
- Glycine
- Magnesium-containing active ingredients
- Milk solids, dried
- Phosphate-containing active ingredients
- Potassium-containing active ingredients
- Sodium-containing active ingredients
- Silicates
- Tartrate-containing active ingredients

As mentioned previously, the OTC analgesic combination products indicated for hangover or overindulgence are referenced across four different OTC monographs:

- Final Monograph (FM) Antacids Products for OTC Human Use (21 Code of Federal Regulations (CFR) 331): Published on June 4, 1974 establishing conditions under which OTC orally-administered drug products could be sold for the relief of heartburn, sour stomach, and acid indigestion
- FM Stimulant Drug Products for OTC Human Use (21 CFR 340): Published on February 29, 1988 establishing conditions under which OTC orally-administered drug

products containing caffeine could be sold as a stimulant to help restore mental alertness, wakefulness from fatigue or drowsiness

- Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for OTC Human Use (21 CFR 343): Published on November 16, 1988 establishing conditions under which OTC orally-administered combination drug products containing an analgesic and an antacid for the relief of heartburn, upset stomach, and sour stomach when accompanied with headache or body aches and pains; upset stomach with headache from overindulgence in food or drink; and headache, body aches, and pains alone
- TFM for Overindulgence in Food and Drink for OTC Human Use (21 CFR 357): Published on December 24, 1991 establishing conditions under which OTC orally-administered drug products could be sold for the relief of symptoms related to overindulgence. Due to significant overlap with other rulemakings in the OTC monographs (i.e., Antacid, Stimulant, and IAAA), FDA proposed amending the final monographs for Antacid and Stimulants, and the TFM for IAAA to include appropriate conditions for relief of hangover symptoms. Specifically, FDA proposed that the antacid-analgesic combination drug products be indicated for the temporary relief of minor aches and pains with heartburn, sour stomach, acid indigestion, and upset stomach associated with these symptoms: "hangover or overindulgence in food and drink"; and the analgesic-caffeine combination drug products be indicated for: "the 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." Hangover is a lay word commonly used to describe a constellation of symptoms encountered several hours after ingesting large amounts of alcohol on a sporadic basis. The term hangover is not defined in Stedman's Medical Dictionary (Lippincott, Williams, and Wilkins). In 1982, in order to form a working definition of "hangover", the Advisory Committee Review Panel on OTC Miscellaneous Internal Drug Products (47 FR 43540-43559) defined the term hangover as a condition consisting of complex symptoms involving the gastrointestinal, neurologic, and metabolic system that follows recent acute excessive alcohol ingestion. The symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression and irritability.

In 2014, DNDP identified a trend of increased hemorrhages associated with effervescent aspirin-antacid combination drug products from the FDA Adverse Events Reporting System (FAERS) database. Therefore, DNDP requested a comprehensive review by the Office of Surveillance and Epidemiology (OSE), which was conducted in 2014. In 2016, another OSE review was requested in preparation for this NDAC/DSaRM meeting.

The primary objective of the OSE review was to identify serious adverse events associated with OTC analgesic-antacid combination products indicated for overindulgence (i.e. upset stomach), primarily major bleeding events associated with the aspirin or salicylate component. However, for completeness, a broader scope of review by OSE was requested to include analgesic-stimulant combination products indicated for the treatment of hangover as well as liver toxicity events associated with the acetaminophen-antacid combination

products for the treatment of hangover symptoms under the Overindulgence monograph. The 2016 OSE review, analyzed five years of drug utilization patterns, four decades of case reports identified in the literature, the FAERS database, and published safety data related to the use of OTC aspirin-antacids, acetaminophen-antacids, and analgesic-caffeine combinations.

- ***Previous Analysis of Gastrointestinal Bleeding Risk***

FDA previously analyzed postmarketing case reports of stomach bleeding collected by the FAERS database from 1998-2001. FDA determined from these data that serious stomach bleeding can occur even when nonsteroidal anti-inflammatory drugs (NSAIDs) are used according to the warnings and directions on the Drug Facts Label (DFL). In 2002, FDA Nonprescription Drugs Advisory Committee met and unanimously agreed that the evidence of risk associated with unintentional NSAIDs overuse warrants a stomach bleeding warning. Hence, in 2006, Proposed Rulemaking was published in the Federal Register. In 2009, FDA published an Organ-Specific Warnings FM for IAAA drug products that required new labeling warnings to caution consumers with one or more of the following risk factors that they may have a higher chance of severe stomach bleeding with NSAIDs use (74 FR 19385 at 19408 to 19409), including:

- Age 60 years or older
- History of stomach ulcers
- History of bleeding problems
- Take a blood thinning (anticoagulant) or steroid drug
- Take other drugs containing prescription or OTC NSAIDs (aspirin, ibuprofen, naproxen, or others)
- Have 3 or more alcoholic drinks every day while using this product
- Take more or for a longer period of time than directed

The Organ-Specific Warnings FM also required new DFL warnings to caution consumers to ask a doctor before starting an aspirin regimen for cardiovascular indications and to ask a doctor before use if the consumer has a history of stomach problems such as heartburn.

Despite severe stomach bleeding warning on the DFL, FDA continued to receive reports of serious GI safety issues with widely used aspirin-containing antacid products to treat heartburn, sour stomach, acid indigestion, or upset stomach; hence, on June 17, 2016, FDA published a Drug Safety Communication (DSC). The DSC (See Appendix 6 for full DSC) warned consumers about the risk of serious bleeding when using OTC aspirin-containing antacid products to treat heartburn, sour stomach, acid indigestion, or upset stomach and that many other products for these conditions are available that do not contain aspirin. Consumers were advised to read the DFL carefully when purchasing or taking an OTC product to treat heartburn, acid indigestion, or sour or upset stomach.

- ***Previous Analysis of Liver Toxicity Risk***

FDA analyzed data from national databases including emergency departments, hospital discharges, mortality data, poison control centers, and spontaneous postmarketing drug adverse event reports reported through the FAERS database from 1990-2001. In addition, results of acute liver failure studies in the United States that were published by the United States (U.S.) Acute Liver Failure Study Group and case series from the University of Pennsylvania Hospital were analyzed. FDA concluded that unintentional overuse of acetaminophen is associated with a large number of emergency department and hospital admissions and is related to an estimated 100 deaths each year. Hence, the Nonprescription Drug Advisory Committee met in 2002 to discuss OTC IAAA drug products and unanimously agreed that the evidence of risk associated with unintentional overuse warrants a liver injury warning for OTC drug products containing acetaminophen (71 FR 77314 at 77323 to 77324). The committee recommended that the term ‘‘acetaminophen’’ (71 FR 77314 at 77323) appear prominently on the front panel or principal display panel (PDP) of product labeling (so consumers are aware that acetaminophen is present in the products they are using to prevent unintentional overdose). After publishing the Proposed Rulemaking Notice in 2006, the 2009 Organ-Specific Warnings FM was published with new liver warnings that highlight the potential for liver toxicity as follows:

Liver Warning:

- This product contains acetaminophen
- Severe liver damage may occur if you take more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount; with other drugs containing acetaminophen; 3 or more alcohol drinks every day while using this product
- Do not use with any other drug containing acetaminophen (prescription or non-prescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist
- Ask a doctor before use if you have liver disease
- Ask a doctor or pharmacist if you are taking the blood thinning drug warfarin

3.3.2.2 International Actions

According to de Abajo et al. (de Abajo and Rodriguez, 2009) only five (Italy, Austria, Romania, Hungary, and Malta) of 22 continental European Union countries where combination products containing aspirin, sodium bicarbonate and citric acid are marketed have gastric indications. In 2004, the Spanish Agency for Medicines and Medical Devices, after a negative report from its Committee on Safety of Medicines, requested the withdrawal of the aspirin component, leaving it as an antacid drug only.

3.3.3 Review of the Published Literature

In order to assess clinical implications of individual and combination drug products pertaining to the four different Monographs noted above, a review of scientific literature was performed to search for published articles on clinical safety. In addition, a literature search

was performed to assess the effects of alcohol and safety of combining alcohol with acetaminophen or aspirin. The following search terms were used:

- "Gastrointestinal Hemorrhage"[Mesh] OR "gi bleed*" OR "gastrointestinal bleed*" OR "gastrointestinal hemorrag*"
- Alka-Seltzer OR "alka seltzer" OR aspirin AND citrates AND sodium
- "Gastrointestinal Hemorrhage"[Mesh] OR "gi bleed*" OR "gastrointestinal bleed*" OR "gastrointestinal hemorrag*" AND Alka-Seltzer OR "alka seltzer" OR aspirin AND citrates AND sodium
- Aspirin AND (antacid OR antacids)
- Aspirin AND (antacid OR antacids) AND "Gastrointestinal Hemorrhage"[Mesh] OR "gi bleed*" OR "gastrointestinal bleed*" OR "gastrointestinal hemorrag*"
- (antacid OR antacids) AND acetaminophen
- (antacid OR antacids) AND acetaminophen AND "Gastrointestinal Hemorrhage"[Mesh] OR "gi bleed*" OR "gastrointestinal bleed*" OR "gastrointestinal hemorrag*"
- "liver injury" OR "liver injuries" OR "liver failure" OR "liver abnormality" OR "liver abnormalities"
- "liver injury" OR "liver injuries" OR "liver failure" OR "liver abnormality" OR "liver abnormalities" AND (antacid OR antacids) AND acetaminophen
- ("gastrointestinal hemorrhage/chemically induced"[mesh] AND "aspirin/adverse effects"[mesh]) AND (incidence[tw] OR prevalence[tw]) with filters of "10 years", humans, and English
- ((((("cerebral hemorrhage/chemically induced"[mesh] OR "cerebral hemorrhage" OR "cerebral haemorrhage") AND ("Aspirin/adverse effects"[Mesh] OR aspirin)) AND (incidence[tw] OR prevalence[tw])) with filters of "10 years", humans, and English
- (("Hepatitis/chemically induced"[Mesh] OR "Drug-Induced Liver Injury"[Mesh] OR transaminitis) AND "Acetaminophen/adverse effects"[Mesh]) AND (incidence[tw] OR prevalence[tw]) with filters of "10 years", humans, and English
- (("Hepatitis/chemically induced"[Mesh] OR "Drug-Induced Liver Injury"[Mesh] OR transaminitis) AND "Acetaminophen/adverse effects"[Mesh]) AND (incidence[tw] OR prevalence[tw]) AND alcohol with filters of "10 years", humans, and English
- (("caffeine"[MeSH Terms] OR "caffeine"[All Fields]) AND hangover[All Fields]) AND (Review[ptyp] AND "2012/01/30"[PDat]
- (("caffeine"[MeSH Terms] OR "caffeine"[All Fields]) AND ("stomach"[MeSH Terms] OR "stomach"[All Fields] OR "gastric"[All Fields]) AND effects[All Fields]) AND (Review[ptyp] AND "2012/01/30"[PDat]

The literature search was performed on PubMed, EMBASE™ and Google, which combined, produced over 250 articles. In addition, FDA's website was searched extensively for NDAC Meeting Minutes, Code of Federal Regulations, and the Federal Register. The literature search resulted in a list of published articles that fall into one of the following categories that will be the focus of this review:

- Federal Register Publications
- Clinical studies (controlled or non-controlled)

- Case reports/series
- Review articles
- Publications related to alcohol, caffeine, and hangover

For the purposes of this briefing document, references are described below if it provided clinical safety information and implications from using either individual or combined products. OSE's literature review pertained to pharmacoepidemiology and postmarketing safety data.

3.3.3.1 Aspirin-Antacid

Bleeding complications are a major adverse event of aspirin therapy. Upper GI bleeding is the most frequent, clinically relevant aspirin-related bleeding complication (Lanas, 2011). Central nervous system (CNS) bleeding complications, such as intracerebral hemorrhage and subarachnoid hemorrhage, occur relatively less frequently, but are the most serious complications of aspirin therapy (Lanas, 2011). Aspirin reduces cytoprotection of the GI mucosa due to dose-dependent impairment of prostaglandin E_2 synthesis (Beigel, Matetzky, et al. 2007). In addition, aspirin, at doses greater than 30 mg, decreases platelet aggregation due to irreversible inhibition of thromboxane A_2 production (Beigel, Matetzky, et al. 2007).

An aspirin-sodium bicarbonate-citric acid combination product was analyzed by the Medical Letter (The Letter) in April 1973. The Letter stated that this combination product was intensely promoted to the public for the relief of upset stomach. The promotion to physicians emphasized the claims that this combination product works faster than aspirin and without causing gastric irritation. The Letter objected to using this combination product as an antacid since it contains aspirin which may cause gastritis and aggravate the symptoms and pathologic changes of a peptic ulcer. The Letter noted that analgesic-antacid combination may be useful if used for alcohol hangover; however, the Letter emphasized that all forms of aspirin, including this combination product, have been associated with hematemesis and melena when taken shortly after heavy drinking of alcoholic beverages (The Medical Letter, 1973).

Reviewer Comments:
The author(s) did not provide any references for hematemesis and melena associated with an aspirin-sodium bicarbonate-citric acid combination product; however, the Letter was one of the first reviews that outlined potential complications of combining aspirin with an antacid to treat symptoms of upset stomach.

In 1980, Innes et al. (Innes, Ford, et al. 1980) reported a series of ten patients over six years who were admitted to the Eastern General Hospital in Edinburgh, United Kingdom, with acute GI bleeding following ingestion of an aspirin-sodium bicarbonate-citric acid combination product. The authors reported that all of the patients took this combination product for dyspeptic symptoms prior to the clinical onset of GI blood loss. Seven patients required blood transfusions and two underwent emergency surgery. The GI bleeding was due to erosive gastritis in four patients, gastric ulceration in three patients, duodenal

ulceration two patients, and stromal ulceration in one patient. The authors concluded that the use of this combination product as an antacid-analgesic combination drug product may be hazardous in patients with dyspepsia and should not be recommended to treat dyspepsia.

In 1991, Hirschowitz et al. (Hirschowitz and Lanas, 1991) published reports describing the increased risk of GI bleeding with NSAIDs used for the treatment of osteoarthritis and non-arthritis pain. By objective testing, the authors noted that aspirin in comparison to other NSAIDs was more strongly associated with GI bleeding from both ulcer and non-ulcer GI bleeding including colonic bleeding than previously reported.

In 1999, Kapicioglu et al. (Kapicioglu, Cetiner, et al. 1999) performed a placebo-controlled double-blind randomized trial on 30 healthy subjects with single dose of placebo, plain aspirin 500 mg, and aspirin 324 mg combined with citric acid 965 mg and sodium bicarbonate 1825 mg (effervescent aspirin). Endoscopy was performed on all subjects four hours after administering the study drug. Endoscopy results showed average gastric mucosal injury score of 0.2, 2.8, and 2.9 in placebo, aspirin, and effervescent aspirin groups respectively. The authors concluded that their study results suggest that aspirin combined with citric acid and sodium bicarbonate has the same adverse events on gastric mucosa as plain aspirin and caution is advised.

Reviewer Comments:
The authors' study is one of few studies that did a head-to-head comparison between placebo, regular aspirin, and an aspirin-sodium bicarbonate-citric acid combination product. This study helped clarify contradictory information in the literature regarding the effect of effervescent aspirin.

3.3.3.2 Acetaminophen-Antacid

Although allowed under the IAAA monograph, acetaminophen-antacid combination drug products do not appear to be marketed currently in the United States.

According to PubChem (PubChem Compound Database), acetaminophen itself is nontoxic; however, hepatocellular injury is related to the formation of an electrophilic reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI). According to Court et al. (Court, Duan, et al. 2001), at therapeutic doses, acetaminophen is predominantly metabolized by glucuronidation (52-57%) and sulfation (30-44%) conjugation reactions with less than 5% of the drug metabolized by oxidation to NAPQI. In clinical situations involving acute or chronic overuse of acetaminophen (whether unintentional or intentional) or concomitant predisposing factors, the glucuronidation process can become overwhelmed, forcing increased acetaminophen metabolism through the oxidative pathway. When this occurs, the reactive acetaminophen metabolite binds to important hepatic intracellular proteins, resulting in cell death. This process creates acetaminophen-protein adducts that are detectable in serum and may serve as a biomarker of acetaminophen toxicity (Muldrew, James, et al. 2002). Studies suggest that fasting and malnutrition may also be risk factors that lower the threshold for hepatotoxicity (Ali, Boyer, and Bird, 2008), (Ghanem, Perez, et al. 2016).

An overdose (intentional or unintentional) from a widely used pain reliever, acetaminophen, is the leading cause of hepatotoxicity or acute drug-induced liver failure in the western world (Wang, 2014). According to Ghanem et al. (Ghanem, Perez, et al. 2016) the incidence of acetaminophen related liver toxicity has been increasing over the past decades and acetaminophen intoxication is now the most common cause of acute liver failure in the United States, Great Britain, and several other countries in the Europe In 2005, Larson et al. (Larson, Polson, et al. 2005) reported that unintentional acetaminophen overdose accounted for 50% of acute liver failure (ALF) cases in the United States. The acetaminophen-induced hepatocellular injury results in a prolonged rise in liver-derived transaminase and alkaline phosphatase serum levels (Larson, Polson, et al. 2005). Without timely intervention after acetaminophen overdose, fulminant hepatic failure can ensue (Maddrey, 2005). When given early in the hepatotoxic process, oral and/or intravenous N-acetylcysteine can be effective in reducing acetaminophen-induced liver injury. Methionine is approved for treatment of acetaminophen overdose in other countries.

In 2011, King et al. (King, Davis, et al. 2011) reported that in the United States, acetaminophen overdose has surpassed viral hepatitis as the leading cause of ALF and its misuse contributes to more than 30,000 hospitalizations per year. More than half to two thirds of acetaminophen overdoses are unintentional or due to failure to recognize the consequences of exceeding daily maximum dose (King, Davis, et al. 2011).

Watkins et al. (Watkins, Kaplowitz, et al. 2006) in a report of a randomized, single-blind, placebo-controlled, 5-treatment, parallel group, diet-controlled (meals provided) longitudinal study of 145 healthy adults in two U.S. inpatient clinical pharmacology units, showed that healthy adults who took 4 g per day of acetaminophen for two weeks had significantly increased liver enzyme concentrations (>3 Upper Limits of Normal (ULN)) in 31% to 44% of participants. As a consequence of the study, in 2006, the American Liver Foundation recommended that people not exceed 3 g of acetaminophen per day for any prolonged period of time.

Reviewer Comments:
Acetaminophen is readily available in multiple formulations and combinations, which may increase the potential for liver injury since acetaminophen has a narrow therapeutic index. The study by Watkins et al., showed that even healthy subjects who were treated at therapeutic doses for two weeks showed evidence of transaminitis.

3.3.3.3 Alcohol

In the United States, one standard drink of alcohol (12 fluid ounces (fl oz) of beer, 8-9 fl oz of malt liquor, 5 fl oz of table wine, and 1.5 fl oz of distilled spirits (gin, tequila, vodka, whiskey, and rum)) contains roughly 14 g of pure alcohol (NIAAA-NIH).

In 2014, Rocco et al. (Rocco, Compare, et al. 2014) reported that alcohol is a major risk factor for chronic diseases and one of the leading causes of preventable morbidity and

mortality worldwide. It has been estimated that the harmful effects of alcohol result in approximately 2.5 million deaths each year with much of the burden depending on alcoholic liver disease (ALD). It is estimated that approximately 28% of the adult population exhibits a high-risk drinking pattern, such as binge drinking, resulting in an increased risk of developing alcohol dependence (Zakhari and Li, 2007). In Europe, alcohol is the third leading cause of premature death and 6.3% of deaths in 2002 were related to alcohol, twice the world average (Federico, Cotticelli, et al 2015). Each year, a quarter of deaths among males aged 15-29 years and 10% of deaths among young women in Europe are caused by alcohol consumption, and 4-6% of disabilities worldwide are attributable to alcohol (Federico, Cotticelli, et al 2015).

Once ingested, the major site of alcohol (ethanol) absorption is the jejunum and 90% is metabolized by the liver while the rest is excreted directly by the lung, urinary system, or sweat (Liu, 2014). According to Rocco et al. (Rocco, Compare, et al. 2014) growing evidence suggests that alcoholic disease should not be considered limited to the liver but as a true systemic disease including damage to the digestive tract, the central and peripheral nervous systems, the heart and vascular system, the bone and skeletal muscle, the endocrine and immune systems, and disruption of nutritional status and finally cancer. According to World Health Organization Report on Alcohol and Health published in 2011, alcohol abuse is responsible for at least 60 major types of systemic diseases and significantly increases the overall risk of developing cancer (Rocco, Compare, et al. 2014). Virtually all individuals chronically exposed to alcohol develop fatty liver, the earliest response of the liver to alcohol consumption, however; only a minority progress to ALD. The two most important risk factors that increase this susceptablity include the amount and duration of alcohol consumption. Additional risk factors include female sex, obesity, non-sex-linked genetic factors, and tobacco consumption (Rocco, Compare, et al. 2014).

Many factors may explain the pathogenic mechanism of ALD which encompasses a broad specturm of diseases including steatosis, fibrosis, and cirrhosis to hepatocellular carcinoma. It has also been demonstrated that binge drinking increases the risk of ALD and mortality (Testino, Burra, et al. 2014). According to Rocco et al. (Rocco, Compare, et al. 2014) the liver is the main organ responsible for metabolizing ethanol, and it is conceivable that ethanol and its metabolites may exert a direct cytotoxic effect by acting as a hepatotoxin. Hepatic metabolism of the ethanol proceeds via oxidative and non-oxidative pathways. The main steps of the oxidative pathway are mediated by alcohol dehydrogenase and acetaldehyde dehydrogenase that transform ethanol to acetaldehyde and acetaldehyde to acetate, respectively. Acetaldehyde damages liver by directly triggering inflammation, extracellular matrix remodeling and fibrogenesis. Furthermore, acetaldehyde stimulates transforming growth factor-beta signaling in hepatic stellate cells that acquire a pro-fibrogenic and pro-inflammatory profile. Through chemical pathways, alcohol consumption results in significant hypoxia of the perivenous hepatocytes, which are the first ones to show evidence of damage from chronic alcohol consumption. In addition, there is upregulation of cytochrome P450 2E1 in chronic alcohol users. Gut-derived lipopolysaccharide (LPS) is another critical trigger of liver steatosis, inflammation, and fibrosis. Alcohol impairs intestinal barrier leading to increased circulation of endotoxin levels from Gram-negative

bacteria in the gut. Increased circulating bacterial endotoxins bind to CD14 on hepatic Kupffer cells via LPS-binding protein. This leads to complex cascade of reactions resulting in the release of inflammatory cytokines, notably tumor necrosis factor (TNF)-α which in turn sustains liver injury by worsening the gut permeability on one side, and upholding the necro-inflammatory hepatic damage on the other side (Rocco, Compare, et al. 2014). TNF-α is one of the earliest liver responses to injury. Studies with transgenic mice lacking TNF-α receptor and treating mice with antibodies to TNF-α receptor during chronic alcohol exposure have shown TNF-α overproduction plays an important role in the progression of ALD (Liu, 2014)

According to Rocco et al. (Rocco, Compare, et al. 2014) acute and chronic consumption of alcohol can affect the upper GI tract via multiple mechanisms including direct and indirect contact of ethanol and/or its metabolite acetaldehyde with the mucosa as well as by non-alcoholic components of alcoholic beverage (fermentation products). These mechanisms can result in:

- Esophageal and gastric inflammation
- Reduced esophageal sphincter pressure
- Impairment of esophageal and gastric motility
- Alteration of gastric acid output

The authors do note increased prevalence of heartburn, gastro-esophageal reflux disease (GERD), and erosive esophagitis in alcoholics.

In 2015, de Jong et al. (de Jong, Cleveringa, et al. 2015) reported that alcohol consumption damages the gut wall immediately after consumption and continues to do so for up to 2.5 hours. Rocco et al. (Rocco, Compare, et al. 2014), suggest that ethanol damages gastric mucosa and weakens its ability to repair itself by stimulating endothelin-1 secretion which inhibits the synthesis and secretion of nitric oxide and prostaglandin E2. Nitric oxide and prostaglandin E2 promote the secretion of bicarbonate, mediate the adaptive immune protective function, increase protein synthesis and renewal, and enhance the reparability of the damaged gastric mucosa.

Reviewer Comments:
Alcohol has significant effects not only on the liver but the GI system as well. Taking aspirin- or acetaminophen-antacid combination medications may pose a safety risk with alcohol. In addition, the pattern of alcohol use in young adults is concerning with at least a quarter of the young adult population engaging in binge drinking (NIAAA-NIH, Alcohol Facts and Statistics) and a quarter of all deaths among males aged 15-29 years, are due to alcohol and its effects(Federico, Cotticelli, et al. 2015)..

3.3.3.4 Alcohol-Acetaminophen Associated Hepatotoxicity

Larson et al (Larson, Polson, et al. 2005) reported that a third of subjects who presented to the hospital with ALF due to acetaminophen overdose met the criteria for alcohol abuse (>40 g/day in men and >20 g/day in women). Subjects with ALF reporting use of < 4 g

acetaminophen per day were often alcohol abusers (65%) and the amount of daily alcohol consumed was greater than that reported by patients who admitted to taking > 4 g acetaminophen per day. The authors noted that ethanol may still serve as an important co-factor in these lower-dose subjects. This finding was confirmed by case reports in the literature by other authors (Lesser, Vietti, et al. 1986) (Licht, Seeff, et al. 1980).

In 2007, Kuffner et al. (Kuffner, Green, et al. 2007) published results of a prospective double-blind, randomized, placebo-controlled trial involving 443 adult alcoholic subjects who entered two alcohol detoxification centers. The subjects were randomized to acetaminophen 4 g/day or placebo for 3 consecutive days. A total of 308 (258 completed) received acetaminophen and 135 subjects (114 completed) received placebo. Both groups did not differ in demographics. The peak mean alanine aminotransferase (ALT) activity in the acetaminophen and placebo groups were unchanged. Subgroup analyses for subjects presenting with an elevated ALT, subjects fulfilling a diagnosis of alcoholic hepatitis and subjects attaining a peak ALT greater than 200 IU/L showed no statistical difference between the acetaminophen and control groups. One participant who developed an increased international normalized ratio was in the placebo group. The authors concluded that alcoholic patients treated with the maximum recommended daily dose of acetaminophen for three consecutive days did not develop increases in serum transaminases or other measures of liver injury and that treatment of pain or fever for three consecutive days with acetaminophen appears safe in newly abstinent alcoholic patients, such as those presenting for acute medical care.

Draganov et al. (Draganov, Durrence, et al. 2000) reported that chronic moderate to heavy alcohol use potentiates the toxic effects of acetaminophen. Severe hepatotoxicity may occur after ingesting as little at 4 g of acetaminophen in 24 hours. According to the authors, generally, large amounts of alcohol intake with acetaminophen are needed to cause liver injury; however, incidents of liver injury have been reported in moderate “social drinkers”. The authors noted that patients usually took acetaminophen to relieve headaches or hangover symptoms. Many patients are unaware that they ingested the drug, because it may have been one of the components of a cold or a headache medicine. The authors observed that patients with liver injury due to combined use of alcohol and acetaminophen had worse prognosis than patients who overdosed on acetaminophen alone even though the former group may have consumed a lower dose of acetaminophen.

In a review article published in 2000 by Prescott, the author noted that the interaction between alcohol and acetaminophen is complex and many questions remain unanswered. In animal studies, chronic administration of alcohol causes microsomal enzyme induction with increased toxic metabolic activation of acetaminophen and enhanced hepatotoxicity. Conversely, the acute administration of alcohol inhibits this potentially toxic oxidative metabolism of acetaminophen and protects against liver damage. This protective effect disappears when the alcohol is eliminated, and the time interval between the intake of alcohol and acetaminophen is critical. However, in humans, chronic administration of alcohol causes only modest and short-lived induction of the microsomal enzymes. Hence, alcohol could increase or decrease the toxicity of acetaminophen, or have no effect

depending on the timing and duration of alcohol consumption. According to the author, alcohol taken with acetaminophen is likely to protect against liver toxicity and chronic alcoholics should be at their most vulnerable during the first few days of withdrawal. The author noted that the reviews of clinical reports are difficult to interpret because insufficient attention was given to the timing of alcohol intake in relation to the intake of acetaminophen. In the author's opinion, even though the possibility that chronic alcoholics are at increased risk of acetaminophen hepatotoxicity cannot be excluded, the available evidence does not support claims for a major toxic interaction between alcohol and acetaminophen in humans. The author states that further studies are needed, and until such studies are completed, all patients who consume alcohol in excess must continue to be considered at high risk following an overdose of acetaminophen and be treated appropriately (Prescott, 2000).

Reviewer Comments:
Overall review of the literature indicates that there are conflicting data regarding alcohol's effect on acetaminophen metabolism. Some of the publications did not fully extract data regarding the relationship between alcohol and acetaminophen such as time of alcohol intake in relationship to acetaminophen ingestion and the exact amount of alcohol and/or acetaminophen ingestion. However, most of the literature suggests that moderate alcohol consumption may be associated with higher risk of acetaminophen related AEs including liver toxicity. In addition, there is a significant gap of knowledge and data regarding short-term and sporadic use of acetaminophen to treat the symptoms of hangover, particularly after binge drinking of alcohol.

3.3.3.5 Caffeine

According to Griffiths et al. (Griffiths, Juliano, et al. 2003) caffeine is a member of the methylxanthine class of alkaloids and is the most widely used mood-altering drug in the world. The authors noted that more than 60 species of caffeine-containing plants have been identified throughout the world. The most widely used are coffee, tea, cola nut, cacao pod, guarana, and maté. Caffeine is the common name for 1,3,7-trimethylxanthine. It is a weakly basic alkaloid. In the gastric system, caffeine is rapidly and completely absorbed after oral administration with peak levels reached in 30 to 45 minutes. It is readily distributed throughout the body (Griffiths, Juliano, et al. 2003). The literature includes discussions regarding caffeine as a stimulant of the central nervous system, as a diuretic in the renal system, and as a stimulant of gastric secretion and gastric motility (Griffiths, Juliano, et al. 2003). Caffeine has been used as a single medication as a stimulant, or in combination with an analgesic for the relief of headaches, minor aches and pains, or with an analgesic for the relief of hangover symptoms.

A review article in 2014 by Derry et al. (Derry, Derry, et al. 2014) examined several clinical trials from the literature that examined the effect of caffeine when used as an adjuvant with analgesics such as ibuprofen, aspirin, or acetaminophen for several pain conditions (headache, dental pain, postoperative pain, and menstrual pain). The assessment of pain relief varied among the clinical trials reviewed. However, the authors concluded that,

overall, caffeine when used as an adjuvant with analgesics led to an increased proportion of subjects achieving at least 50% maximum pain relief compared to analgesics alone with no increase in serious adverse events. In addition, the authors concluded that it is unlikely that adding a dose of caffeine equivalent to a mug of coffee (65 mg to 200 mg) will be harmful if the recommended dose is not exceeded.

In 1999, Boekema et al. (Boekema, Samsom, et al. 1999) published a review article regarding coffee and its GI effects. The authors reported that coffee is often mentioned as a cause of dyspeptic symptoms; however, literature review by the authors found no association between coffee and dyspepsia even though it is the most frequent adverse event reported after coffee consumption. The authors stated that in some people, caffeinated or decaffeinated coffee had similar GI effects. The authors noted that coffee has been demonstrated to promote gastroesophageal reflux. Coffee stimulates gastrin release and gastric acid secretion, but studies on the effect on lower esophageal sphincter pressure yield conflicting results. The authors found that coffee may prolong relaxation of the proximal stomach leading to slow gastric emptying. However, the authors noted that other studies indicated that coffee does not affect gastric emptying or small bowel transit. Coffee induces cholecystokinin release and gallbladder contraction, which may explain why patients with symptomatic gallstones often avoid drinking coffee.

As stated in the December 24, 1991 Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for OTC Human Use; Proposed Amendment to the Tentative Final Monograph (21 CFR 343), caffeine stimulates gastric secretion of hydrochloric acid.

A review by Sawynok and Yaksh noted that in humans, concurrent intake of caffeine (120 mg) with aspirin (650 mg) led to increased peak plasma concentration of aspirin by 20% and increased area under the plasma concentration-time curve of aspirin by 7%; however, there was no change in plasma $T_{1/2}$ or clearance of salicylate (Sawynok and Yaksh, 1993). The authors did review multiple articles supporting caffeine's augmentative effect with analgesics, i.e., NSAIDs including aspirin and acetaminophen, for pain relief in comparison to analgesics alone.

Palmer et al. (Palmer, Graham, et al. 2010) published a meta-analysis that focused on hepatotoxicity of caffeine-acetaminophen combination products and effects of caffeine on oxidative metabolism of acetaminophen. The authors' review of the effects of the combination of acetaminophen and caffeine on the liver asserted that there are no compelling data to suggest a clinically meaningful increase in hepatotoxicity with use of acetaminophen/caffeine combination products. The authors asserted that the hepatotoxicity from overdoses of acetaminophen results from oxidative metabolism and not caffeine, which did not produce any increase in oxidative metabolism of therapeutic doses of acetaminophen.

Reviewer Comments:
Published literature suggests caffeine augments the effect of pain relievers used for the treatment of acute pain. However, some studies suggested increased dyspepsia when

caffeine is used; caffeine stimulates gastric secretion of hydrochloric acid. Dyspepsia is one of the AEs listed on the DFL of NSAIDs. Some studies suggest that alcohol may damage the integrity of the gut wall and weaken its ability to repair itself. Therefore, it is plausible that combining aspirin or NSAIDs with caffeine may lead to a higher incidence of dyspepsia, especially in the setting of recent alcohol consumption, although there do not appear to be any short-term or sporadic use safety data confirming this possibility.

3.3.4 Conclusion

Analgesic-antacid combination drug products are currently available for the temporary relief of the following:

- Heartburn, acid indigestion, and sour stomach when accompanied with headache or minor aches and pains
- Upset stomach associated with overindulgence in food and drink and related symptoms of heartburn, nausea, fullness, belching and gas
- Upset stomach associated with a hangover

The relationship between aspirin-antacid combination products and major GI bleeding was not evident in the literature during the initial rulemaking process in 1973. However, data from the sponsors and FAERS case reports over the last four decades suggest a relationship between aspirin-antacid combination products and major GI bleeding. In 2009, the DFLs of all NSAIDs and aspirin-antacid combination products were required to add the Stomach Bleeding Warnings and cautioned consumers to ask a doctor before use if the Stomach Bleeding Warnings applied to them or if they had stomach problems such as heartburn. Despite these changes to the DFL, the FAERS database continues to receive case reports of major GI bleeding events.

We were unable to find reports of hepatotoxicity related to acetaminophen-antacid combination drug products since they do not appear to be marketed in the United States. Although these products are not currently marketed, as long as this combination remains GRASE in the monograph, products may be introduced into the U.S. market at any time. As such, the question of safety remains relevant for consideration. As noted in this memorandum, the literature contains conflicting data on the relationship between alcohol and acetaminophen metabolism. However, most of the literature suggests that moderate alcohol consumption may be associated with a higher risk of acetaminophen related AEs including liver toxicity.

Stimulant-analgesic combination products are indicated for the temporary relief of minor aches and pain associated with a hangover or to help restore mental alertness/wakefulness when experiencing fatigue or drowsiness associated with a hangover. The FAERS database did not receive any GI bleeding events reported for caffeine-aspirin combination products or hepatotoxicity case reports for caffeine-acetaminophen combination products indicated for hangover. However, lack of case reports related to the use of these combination products does not indicate that these products are completely safe to use for current indications since underreporting may occur, particularly for OTC products. As noted in this memorandum,

caffeine may increase symptoms of dyspepsia. Combining caffeine with aspirin or NSAIDs may further increase the symptoms of dyspepsia.

Alcohol has significant effects on the liver, and it may cause esophageal and gastric inflammation and weaken the ability of the esophageal and gastric mucosa to repair itself. Acetaminophen is a widely used pain reliever and is the leading cause of drug-induced liver injury in the United States. Hence, consumers who use acetaminophen based combination product(s) in the setting of recent excessive alcohol intake may increase their chances of liver injury. Based on the above literature review, the rationality of the use of caffeine combined with either one of the two classes of analgesics (aspirin and acetaminophen) for the treatment of hangover from excessive alcohol consumption is called into question and will be a subject for discussion at the joint Nonprescription Drugs Advisory Committee (NDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) meeting.

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4 Appendices

4.1 Appendix 1: List of Active Ingredients for Antacid and Internal Analgesic Monographs

Antacid Ingredients:

Aluminum carbonate

Aluminum hydroxide

Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid

Aluminum phosphate

Dihydroxyaluminum sodium carbonate

Bicarbonate-containing active ingredients

Bismuth aluminate

Bismuth carbonate

Bismuth subcarbonate

Bismuth subgallate

Bismuth subnitrate

Calcium-containing active ingredients

Citrate-containing active ingredients

Glycine (aminoacetic acid)

Hydrate magnesium aluminate activated sulfate

Magaldrate

Magnesium aluminosilicates

Magnesium carbonate

Magnesium glycinate

Magnesium hydroxide

Magnesium oxide

Magnesium trisilicate

Milk solids, dried

Aluminum phosphate

Mono or dibasic calcium salt

Tricalcium phosphate

Potassium bicarbonate

Sodium potassium tartrate

Sodium bicarbonate

Tartrate acid or its salts

Internal Analgesic Ingredients:

Acetaminophen

Aspirin

Buffered aspirin*

Carbaspirin calcium*

Choline salicylate*

Magnesium salicylate*

Sodium salicylate*

*Only acetaminophen and aspirin are GRASE for the antacid-analgesic combination products

4.2 Appendix 2: Drug Utilization Data Table and Database Descriptions

Table 4.2.1 Nationally estimated number of packages[1] sold for combination analgesic/caffeine products from manufacturers to U.S. retail outlets, August 1, 2011 – July 31, 2016

	Aug 2011-July 2012		Aug 2012-July 2013		Aug 2013-July 2014		Aug 2014-July 2015		Aug 2015-July 2016	
	Packages	*Share*	Packages	*Share*	Packages	*Share*	Packages	*Share*	Packages	*Share*
	N	%	N	%	N	%	N	%	N	%
Grand Total	**21,355,857**	***100.0%***	**22,545,999**	***100.0%***	**22,130,513**	***100.0%***	**22,510,809**	***100.0%***	**20,801,632**	***100.0%***
acetaminophen/aspirin/caffeine	**13,722,695**	***64.3%***	**14,683,690**	***65.1%***	**14,497,219**	***65.5%***	**13,756,919**	***61.1%***	**12,118,328**	***58.3%***
EXCEDRIN MIGRAINE	4,351,178	*31.7%*	7,368,301	*50.2%*	7,216,510	*49.8%*	7,363,547	*53.5%*	6,116,028	*50.5%*
EXCEDRIN EX STR	4,454,907	*32.5%*	2,607,190	*17.8%*	3,563,017	*24.6%*	3,456,543	*25.1%*	2,763,246	*22.8%*
ASA/APAP/CAF	3,942,084	*28.7%*	3,331,200	*22.7%*	2,274,443	*15.7%*	1,816,177	*13.2%*	2,208,962	*18.2%*
GOODYS	362,952	*2.6%*	676,627	*4.6%*	1,129,606	*7.8%*	972,085	*7.1%*	890,058	*7.3%*
VANQUISH	251,666	*1.8%*	301,056	*2.1%*	101,979	*0.7%*	101,009	*0.7%*	59,431	*0.5%*
PAIN RELIEVER PLUS	62,759	*0.5%*	55,338	*0.4%*	43,949	*0.3%*	47,273	*0.3%*	43,879	*0.4%*
MIGRAINE	82,743	*0.6%*	20,503	*0.1%*	3,550	*0.0%*	19	*0.0%*	36,637	*0.3%*
BACK PAIN-OFF	0	*0.0%*	0	*0.0%*	4	*0.0%*	88	*0.0%*	60	*0.0%*
PAIN OFF			274	*0.0%*	21	*0.0%*	18	*0.0%*	27	*0.0%*
BAYER MIGRAINE	119	*0.0%*	323,114	*2.2%*	164,081	*1.1%*	0	*0.0%*	0	*0.0%*
GOODYS MIGRAINE	0	*0.0%*	48	*0.0%*	59	*0.0%*	0	*0.0%*	0	*0.0%*
EXCEDRIN MENSTRUAL	214,287	*1.6%*	39	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
acetaminophen/caffeine	**4,718,630**	***22.1%***	**4,839,700**	***21.5%***	**4,683,482**	***21.2%***	**5,752,667**	***25.6%***	**5,859,257**	***28.2%***
MIDOL	1,728,326	*36.6%*	2,120,477	*43.8%*	2,086,717	*44.6%*	2,352,361	*40.9%*	2,233,723	*38.1%*
MIDOL MENSTRUAL	1,646,507	*34.9%*	1,946,832	*40.2%*	1,789,519	*38.2%*	2,086,118	*36.3%*	1,979,918	*33.8%*
EXCEDRIN TEN HDCHE	450,537	*9.6%*	85	*0.0%*	24,310	*0.5%*	629,847	*11.0%*	670,037	*11.4%*
APAP/CAF/PYRL	601,961	*12.8%*	501,051	*10.4%*	462,920	*9.9%*	515,020	*9.0%*	659,749	*11.3%*
APAP/CAF	41,570	*0.9%*	271,255	*5.6%*	320,016	*6.8%*	169,321	*2.9%*	165,634	*2.8%*
MIDOL COMPLETE	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	150,196	*2.6%*
ARTHRITIN PLUS	10	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
aspirin/caffeine	**2,914,532**	***13.6%***	**3,022,609**	***13.4%***	**2,949,812**	***13.3%***	**3,001,223**	***13.3%***	**2,824,047**	***13.6%***
BC FAST PAIN RLF	714,126	*24.5%*	851,670	*28.2%*	1,305,712	*44.3%*	1,284,592	*42.8%*	1,366,738	*48.4%*
BAYER BACK/BDY PAIN	696,072	*23.9%*	819,294	*27.1%*	876,149	*29.7%*	1,085,422	*36.2%*	873,403	*30.9%*
ANACIN	348,816	*12.0%*	320,642	*10.6%*	333,935	*11.3%*	244,109	*8.1%*	207,415	*7.3%*
BC FAST PAIN ARTH	139,292	*4.8%*	162,876	*5.4%*	242,399	*8.2%*	230,007	*7.7%*	207,040	*7.3%*
ASPIRIN/CAF	126,088	*4.3%*	165,882	*5.5%*	112,837	*3.8%*	107,243	*3.6%*	129,038	*4.6%*
BC	774,606	*26.6%*	584,531	*19.3%*	40,525	*1.4%*	40,899	*1.4%*	34,385	*1.2%*
STANBACK	2,588	*0.1%*	3,015	*0.1%*	3,307	*0.1%*	4,775	*0.2%*	5,230	*0.2%*
ARTHRITIS BC	101,463	*3.5%*	83,537	*2.8%*	1,060	*0.0%*	993	*0.0%*	798	*0.0%*
ANACIN MAX STR	11,460	*0.4%*	31,120	*1.0%*	33,882	*1.2%*	3,183	*0.1%*	0	*0.0%*
BAYER QK RLS CRYS	0	*0.0%*	2	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
COPE	20	*0.0%*	40	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
ALKA-SEL WAKE UP CALL	1	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*

Source: IMS Health, IMS National Sales Perspectives™. Aug 2011 - Jul 2016. Extracted November 2016. File: NSP 2016-1449 Overindulgence products 11-4-16.xlsx

[1]Packages refers to the number of pill bottles or blister packs sold

***** QuintilesIMS estimates their projections of the total over-the-counter (OTC) market to be approximately 50%

QuintilesIMS, IMS National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, health maintenance organizations, long-term care facilities, home health care, and other miscellaneous settings. QuintilesIMS estimates their projections of over-the-counter (OTC) products to be approximately 50%. This reduced capture is due to non-Rx data not always being fully reported by our data suppliers, and the unique distribution patterns of OTCs through data suppliers not reporting to IMS.

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow-up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

4.3 Appendix 3: Line Listing of FAERS Cases for Effervescent Aspirin Products Including FAERS Case Numbers, FAERS Version Numbers, and Manufacturer Control Numbers (n=20)

Table 4.3.1: Line Listing of FAERS Cases of Hemorrhagic Events with Effervescent ASA/Antacid Products (n=20)

	FAERS Case #/ Version	Age in Years/ Sex	Reported Alka-Seltzer product	Initial FDA received date	Alka-Seltzer indication	Location/Major bleeding event	Trans-fusion?	Risk factors for bleed	Manufacturer Number
Fatal Case									
1)	4248197/1	69/F	Unknown	11/1/1970	Unknown	Unspecified/ "massive" GI bleed	Yes	Concomitant aspirin use	Not applicable
Non-Fatal Cases									
2)	3448010/1	66/M	Unknown	3/13/2000	Unknown	Unspecified/ "severe" GI bleed	Yes	Concomitant naproxen use	6326650
3)	3834263/1	n/a	Original	8/26/2002	Abdominal pain and indigestion	Unspecified/GI bleed	Yes	None reported	Not applicable
4)	4046593/1	69/M	Unknown	12/22/2003	Respiratory infection	Upper GI bleed/Gastric polyps	Yes	Concomitant warfarin and aspirin use	US-BRISTOL-MYERS SQUIBB COMPANY-12455267
5)	4277157/1	75/F	Unknown	6/1/1973	Abdominal discomfort	Upper GI bleed,/ Hematemesis/ melena	None reported	Concomitant aspirin use	Not applicable
6)	4280387/1	24/M	Unknown	9/1/1973	GI pain	Upper GI bleed/Duodenal ulcer	None reported	Being treated for GI issues	Not applicable
7)	5352929/1	79/M	Unknown	1/4/1996	Headache	Unspecified/GI bleed	None reported	Concomitant aspirin and Advil use	Not applicable
8)	5657857/1	26/M	Unknown	10/22/2004	Unknown	Upper GI bleed/Mallory-Weiss Syndrome /hematemesis	Yes	History of alcohol abuse	200412887GDS
9)	5787970/2	91/F	Unknown r	4/21/2005	Heartburn/ flatulence	Upper GI bleed /Gastrointestinal hemorrhage	Yes	None reported	200510186BCA
10)	6143536/1	30/M	Unknown	10/9/2006	Unknown	Unspecified/GI bleed	Yes	Concomitant aspirin use	US-BAYER-200613874BCC
11)	6214387/1	45/M	Unknown	1/12/2007	Unknown	Upper GI bleed/Duodenal ulcer	None reported	Concomitant indomethacin, naproxen, ibuprofen, and prednisone use	US-ROXANE LABORATORIES, INC-2007-DE-00138GD
12)	6770550/2	68/M	Original	9/25/2008	Digestion Aid	Unspecified/Blood loss during surgery	Yes	Concomitant clopidogrel and aspirin use	US-BAYER-200813775BCC
13)	7248223/2	66/M	Unknown	1/18/2010	Unknown	Lower GI bleed/ Rectal hemorrhage	None reported	None reported	US-BAYER-201010390BCC
14)	7391433/1	89/M	Lemon-lime	5/18/2010	Heartburn	Lower GI bleed/ Rectal bleeding	Yes	Concomitant aspirin use	US-BAYER-201015210BCC
15)	7586155/1	73/M	Unknown	9/14/2010	Unknown	Unspecified/ "bleeding internally"	Yes	Concomitant ibuprofen use	US-WYE-H07162208
16)	8088537/2	61/F	Original	8/15/2011	Hayfever	Lower GI bleed/ Rectal bleeding	None reported	None reported	US-BAYER-2011-067174

17)	8266809/1	86/F	Unknown	11/29/2011	Stomach problems	Upper GI bleed/ Hematemesis/ melena	None reported	Concomitant aspirin use	US-BAYER-2011-114040
18)	9788089/1	36/M	Unknown	12/27/2013	Cold	Upper GI bleed/Gastric ulcers	Yes	Concomitant ibuprofen use	Not applicable
19)	9983615/1	55/F	Original	3/7/2014	Indigestion	Upper GI bleed/Gastric ulcers	None reported	None reported	US-BAYER-2014-033191
20)	10476022/1	n/a/M	Original	9/25/2014	Unknown	Upper GI bleed/ Haematemesis/ duodenal ulcer	None reported	None reported	US-BAYER-2014-140079

4.4 Appendix 4: Summary of Randomized Controlled Clinical Trials

Table 4.4.1: Summary of Studies of Aspirin (ASA)-Antacid Combination Products

Meta-analysis

Author (Year) Funding	Exposure (type)	Outcome	Cohort Size	Safety findings	Comment
Lampl (2007) Co-author: Bayer affiliation	RCTs of 1,000 mg efferv ASA, sumatriptan, and placebo acute migraine	Pain relief and safety	374, 356, and 516 patients in trials	• Adverse events: 12% efferv ASA, 16.2% sumatriptan, 7.1% placebo. • Investigators reported drug-reaction adverse events as: 4.3% efferv ASA, 8.6% sumatriptan, 3.7% placebo. • Most common adverse events, efferv ASA: Gastrointestinal, 3.6%; Nervous system, 1.8%.	• Included 3 double-blinded, randomized, placebo-controlled trials: Diener (2004), EMSASI group (2004), and Lange (2004). • No bleeding events reported. • Adverse events were classified as drug-related by investigators: problem of subjectivity, inability to distinguish between adverse events related to migraines vs. drugs, inter-investigator variation in classification. • Short follow-up periods and infrequent doses, so could not assess effects of chronic use. • The meta-analysis reported higher numbers in these trials than what were actually analyzed by the studies (details for each study are given below)

Randomized controlled clinical trials (RCTs)

Author (Year)	Exposure	Outcome	Cohort Size	Safety findings	Comments
Diener (2004) Germany Sponsor: Bayer AG	1,000 mg efferv ASA, 50 mg sumatriptan, and efferv placebo	Pain relief and safety	516 migraine patients randomized; 433 were analyzed.	• No major adverse events reported. • Adverse events: 12.9% of efferv ASA patients, 14.1% of sumatriptan patients, 10.5% of placebo patients. • Gastrointestinal adverse events: 3.4% in efferv ASA group, 5.2% of sumatriptan group, 4.6% of placebo group.	• Double-blinded, randomized, placebo-controlled trial. • Efferv placebo and a placebo tablet resembling sumatriptan were used. • Adverse drug events: inability to distinguish between adverse events related to migraines vs. drugs. • Investigator judgments of adverse events: problem of subjectivity, inter-investigator variation. • Single dose and short follow-up period, so could not assess effects of chronic use.

EMSASI group (2004) (Diener) Germany, Italy, Spain Sponsor: Bayer AG	1,000 mg efferv ASA, 50 mg sumatriptan, 400 mg ibuprofen, and matching placebos that looked like active drugs	Pain relief and safety	356 migraine patients; 312 were included in analysis	• 2 serious adverse events (renal colic in efferv ASA group and perforated ulcer in ibuprofen group). • Adverse events: 16.2% efferv ASA, 19.8% sumatriptan, 12.3% ibuprofen, 14.4% placebo. • Adverse events considered as drug-related: 4.1% efferv ASA, 6.6% sumatriptan, 5.7% ibuprofen, 4.5% placebo.	• Double-blinded, crossover, randomized, placebo-controlled trial. Patients received 3 different group assignments. • Effervescent placebo and placebos that matched other drugs were used. • No bleeding events reported. • Adverse events were judged by whether they were related to drugs by investigators: problem of subjectivity, inability to distinguish between adverse events related to migraines vs. drugs, inter-investigator variation in classification. • Excluded patients with history of peptic ulcers or gastric bleeding. • Excluded 44 patients due to lack of compliance, so not pure intention-to-treat analysis. • Short follow-up periods, so could not assess effects of chronic use.

Lange (2004) Germany Sponsor: Bayer	1,000 mg efferv ASA vs. efferv placebo	Pain relief and safety	374 migraine patients, of which 343 were analyzed	• No serious adverse events except in one patient who was not treated by efferv ASA or placebo. • Patients reporting adverse events: 14/169 (8.3%) in efferv ASA group, 5/174 (2.9%) in placebo group, 7/31 (22.6%) in randomized but untreated group. • Investigators counted 18/169 adverse events in efferv ASA group and 9/174 in placebo group, but considered difference as clinically irrelevant. • 3 digestive system events in efferv ASA group, none in placebo group.	• Double-blinded, randomized, placebo-controlled trial. • Effervescent placebo was used. • No bleeding events reported. • Assessment of clinical irrelevance is too sweeping. • Short follow-up periods, so could not assess effects of chronic use. • Analyzed patients' safety events among those not complying with trial after randomization, which reduced potential for bias.
Eccles (2003) United Kingdom and Sweden Sponsor: Likely Bayer	800 mg efferv ASA vs. efferv placebo	Pain relief and safety	139 patients in efferv ASA group, 133 in efferv placebo group; all had sore throats as a result of colds	• No serious adverse events. • 17 patients with adverse events in each treatment group. • Efferv ASA: 2 nosebleeds, 3 abdominal pain, 2 nausea, 5 headaches. • Placebo: 1 nosebleed, 2 abdominal pain, 1 nausea, 5 headaches.	• Double-blinded, randomized, placebo-controlled trial. • Effervescent placebo used. • No bleeding events reported. • Short follow-up periods (4 days), so could not assess effects of chronic use. • Slightly more nosebleeds and gastrointestinal symptoms in efferv ASA group compared with placebo group.

Reiff (1988) USA Sponsor: Miles Laboratories	ASA 324 mg, efferv ASA (324 mg, 1,916 sodium bicarbonate, 1,000 mg citric acid), efferv buffer (placebo), water only, vs. no rinsing, 21-day treatment period, twice daily	Gingival inflammation measured by sulcus bleeding index	50 (10 per group)	No safety findings were reported	• Double-blinded, randomized, placebo-controlled trial. • Effervescent placebo was used. • Adverse drug reactions were not reported. • 21-day treatment and follow-up period, so could not assess effects of chronic use. • Small numbers limited statistical power.
Langemark (1987) Denmark Funding source not reported	648 mg ASA, 648 mg efferv ASA, tablet placebo, efferv placebo	Pain relief, safety	47 migraine headache patients	Adverse effects were mild. No differences between efferv aspirin and efferv placebo for all adverse events or GI adverse effects (nausea, heartburn, vomiting, colic).	• Double-blind, crossover, so that patients took each of 4 treatments for 4 migraine episodes. • Effervescent placebo was used. • Excluded patients with history of gastritis or peptic ulcer. • Low doses and short follow-up periods precluded detection of adverse effects from chronic use.
Tfelt-Hansen (1984) Denmark Funding source unclear; some involvement from Miles Laboratories	650 mg efferv ASA + 10 mg efferv metoclopramide, 650 efferv ASA, efferv placebo	Pain relief and safety	118 migraine headache patients (16 patients excluded due to non-compliance, so analyzed 102 patients)	• Reported by Diener (2006), but not in published paper. Adverse effects: 8% efferv ASA, 11.7% efferv ASA and metoclopramide, 12.4% placebo. • Paper reported 7 adverse events in efferv ASA group, 11 in efferv ASA + metoclopramide group, 12 in placebo group.	• Double-blind, cross over, so that patients took up to 3 treatments for 3 separate migraine episodes. • Effervescent placebo was used. • Low doses and short follow-up periods precluded detection of adverse effects from chronic use. • Difficult to distinguish migraine symptoms from adverse events associated with drugs. • Not pure intention-to-treat analysis due to exclusions.

Lange (2000) Germany Sponsor: Bayer	1,000 mg efferv ASA vs. efferv placebo	Pain relief and safety	374 migraine patients, of which 343 were analyzed	▪ No serious adverse events except in one patient who was not treated by efferv ASA or placebo. ▪ Patients reporting adverse events: 14/169 (8.3%) in efferv ASA group, 5/174 (2.9%) in placebo group, 7/31 (22.6%) in randomized but untreated group. ▪ Investigators counted 18/169 adverse events in efferv ASA group and 9/174 in placebo group, but considered difference as clinically irrelevant. • 3 digestive system events in efferv ASA group, none in placebo group.	• Double-blinded, randomized, placebo-controlled trial. • Effervescent placebo was used. • No bleeding events reported. • Assessment of clinical irrelevance is too sweeping. • Short follow-up periods, so could not assess effects of chronic use. • Analyzed patients' safety events among those not complying with trial after randomization, which reduced potential for bias.
Eccles (2003) United Kingdom and Sweden Sponsor: Likely Bayer	800 mg efferv ASA vs. efferv placebo	Pain relief and safety	139 patients in efferv ASA group, 133 in efferv placebo group; all had sore throats as a result of colds	▪ No serious adverse events. ▪ 17 patients with adverse events in each treatment group. ▪ Efferv ASA: 2 nosebleeds, 3 abdominal pain, 2 nausea, 5 headaches. ▪ Placebo: 1 nosebleed, 2 abdominal pain, 1 nausea, 5 headaches.	• Double-blinded, randomized, placebo-controlled trial. • Effervescent placebo used. • No bleeding events reported. • Short follow-up periods (4 days), so could not assess effects of chronic use. • Slightly more nosebleeds and gastrointestinal symptoms in efferv ASA group compared with placebo group.

Reiff (1988) USA Sponsor: Miles Laboratories	ASA 324 mg, efferv ASA (324 mg, 1,916 sodium bicarbonate, 1,000 mg citric acid), efferv buffer (placebo), water only, vs. no rinsing, 21-day treatment period, twice daily	Gingival inflammation measured by sulcus bleeding index	50 (10 per group)	No safety findings were reported	• Double-blinded, randomized, placebo-controlled trial. • Effervescent placebo was used. • Adverse drug reactions were not reported. • 21-day treatment and follow-up period, so could not assess effects of chronic use. • Small numbers limited statistical power.
Langemark (1987) Denmark Funding source not reported	648 mg ASA, 648 mg efferv ASA, tablet placebo, efferv placebo	Pain relief, safety	47 migraine headache patients	Adverse effects were mild. No differences between efferv aspirin and efferv placebo for all adverse events or GI adverse events (nausea, heartburn, vomiting, colic).	• Double-blind, crossover, so that patients took each of 4 treatments for 4 migraine episodes. • Effervescent placebo was used. • Excluded patients with history of gastritis or peptic ulcer. • Low doses and short follow-up periods precluded detection of adverse effects from chronic use.
Tfelt-Hansen (1984) Denmark Funding source unclear; some involvement from Miles Laboratories	650 mg efferv ASA + 10 mg efferv metoclopramide, 650 efferv ASA, efferv placebo	Pain relief and safety	118 migraine headache patients (16 patients excluded due to non-compliance, so analyzed 102 patients)	• Reported by Diener (2006), but not in published paper. Adverse effects: 8% efferv ASA, 11.7% efferv ASA and metoclopramide, 12.4% placebo. • Paper reported 7 adverse events in efferv ASA group, 11 in efferv ASA + metoclopramide group, 12 in placebo group.	• Double-blind, crossover, so that patients took up to 3 treatments for 3 separate migraine episodes. • Effervescent placebo was used. • Low doses and short follow-up periods precluded detection of adverse effects from chronic use. • Difficult to distinguish migraine symptoms from adverse events associated with drugs. • Not pure intention-to-treat analysis due to exclusions.

Table 4.4.2: Summary of Studies of Analgesic-Caffeine Combination Products					
Meta-analyses and Systematic Reviews					
Author (Year) Funding	**Exposure (type)**	**Outcome**	**Cohort Size**	**Safety findings**	**Comment**
Derry (2015) Sponsor: The National Institute for Health Research, United Kingdom	Meta-analysis of 4 studies of ibuprofen-caffeine combinations; included 200 mg ibuprofen/100 mg caffeine and 100 mg ibuprofen/100 mg caffeine.	Postoperative pain relief and safety.	336 participants: 174 treated with active drug and 162 on placebo.	• 200/100 RCTs: People with an adverse event: 11% ibuprofen-caffeine, 6% placebo. • 100/100 RCTs: People with an adverse event: 14% ibuprofen-caffeine, 8% placebo. • No serious adverse events in either treatment group. • RR for people with an adverse event taking 200/100 combination vs. placebo: 1.86 (0.91-3.79) • RR for 100/100 combination vs. placebo: 1.80 (0.83-3.90)	• All studies randomized and double-blinded. • No other analgesic-caffeine combinations studied other than ibuprofen-caffeine. • 2 studies: dental surgery; 2 studies: post-episiotomy pain. • Doses were 200 mg ibuprofen + 100 mg caffeine or 100 mg ibuprofen + 100 mg caffeine. • Specific adverse events were not presented. • Short-term trials of acute pain had limited ability to detect adverse events, especially those that result from chronic use. • Limited statistical power to detect serious adverse events due to small numbers studied and rarity of events. • Combination drugs were sold only in South America at time of meta-analysis.

Moore (2015) Sponsor: The Oxford Pain Relief Trust (charity, United Kingdom)	Meta-analysis of RCTs of over-the-counter analgesics, including studies of ibuprofen-caffeine combination drugs.	Postoperative pain relief and safety.	See Derry (2015)	• See Derry (2015) for adverse event percentages. • Risk ratio (RR) for participants taking ibuprofen-caffeine with at least one adverse event: 2.2 (1.03-4.9) • Number Needed to Harm: 19 (8.9-220) • Only other analgesic with signif increased RR for people with an adverse event was ASA 1000 mg: 1.6 (1.1-2.3). People with adverse event: 26% ASA vs. 12% placebo.	• See Derry (2015) for details. • Unclear why RRs in Derry (2015) and Moore (2015) differ. • Same limitations as listed for Derry (20-15), including short-term trials and limited statistical power.
Derry (2014) Sponsor: The National Institute for Health Research, United Kingdom	Meta-analysis of RCTs of analgesic-caffeine combinations vs. analgesics alone for ASA, acetaminophen, ibuprofen, diclofenac, tolfenamic acid	Pain relief and safety	4,262 participants from 27 separate comparisons	• 2 cases of serious adverse events in Diener (2005) RCT described separately.	• Meta-analysis did not examine safety in detail and did not consider 2 observed serious adverse events as drug-related. • Short-term trials of acute pain had limited ability to detect adverse events, especially those that result from chronic use.

Table 4.4.2 (continued)

Randomized controlled clinical trials (RCTs)					
Author (Year)	**Exposure**	**Outcome**	**Cohort Size**	**Safety findings**	**Comments**
Damman (2004) Germany Sponsor: Bayer	2 tablets 3 times daily for a total of 10 doses: 250 mg ASA/200 mg acetaminophen/50 mg caffeine vs. plain ASA, chewable ASA, or effervescent ASA.	Lanza score (GI erosions and petechiae, which are small spots of bleeding), Petechiae, Gastric microbleeding.	17 healthy subjects randomized to receive each of 4 treatments and upper endoscopy	• Lanza score, Petechiae, and Gastric bleeding: ASA/acetaminophen/caffeine combo and plain ASA had signif higher scores (adverse effects) compared with efferv ASA.	• RCT crossover, blinded investigator; unclear if patients were blinded. • Upper endoscopies done at baseline before each drug and then on 4th day after received 10 doses of each of the study drugs. • Mucosal erosions, petechiae, gastric microbleeding: all rare events. • Short-term exposure limited ability to find effects from chronic use, but 10 doses more useful than single dose. • Data presented in terms of means, so unclear what percentage of subjects had evidence of adverse effects on GI system from analgesics. • ASA/acetaminophen/caffeine combo: hard to generalize to ASA/caffeine or acetaminophen/caffeine. • Sponsor had financial interest in observing benefit for efferv ASA.

Pini (2012) Italy Sponsor: Italian League of Cephalgic Patients	acetaminophen 1,000 mg/caffeine 130 mg vs. Sumatriptan 50 mg (SUM)	Pain relief and safety	92 migraine patients receiving 264 treatments	• Poor tolerability: 8.4% in acetaminophen/caffeine vs. 9.7% in SUM. • Patients with adverse effects: 47% of acetaminophen/caffeine group vs. 58% of SUM group. • GI symptoms: 42% of acetaminophen/caffeine group vs. 40% of SUM group.	• RCT crossover, double-blinded. • Each patient was treated 3 times, allocated to receiving either 2 acetaminophen/caffeine and 1 SUM or 1 acetaminophen/caffeine and 2 SUM. • Adverse events were recorded by filling in a symptom checklist hourly for 4 hours after each treatment. Patients rated tolerability. • Short-term exposure limited ability to find effects from chronic use.
Diener (2005) Germany Sponsor: Boehringer Ingelheim	2 tablets of ASA 250 mg/ acetaminophen 200 mg /caffeine 50 mg vs. ASA/acetaminophen, ASA alone, acetaminophen alone, caffeine alone, or Placebo	Pain relief and safety	1,983 headache (tension or migraine) patients	▪ Adverse events: 8% in ASA/acetaminophen/ caffeine group, 3.6% in Placebo group, 5.8% in acetaminophen alone group, 6.3% in caffeine alone group, and 9.7% in ASA alone group, • GI adverse events: 4.5% in ASA/acetaminophen/caffeine group, 4.7% in ASA alone group, 2.1% in Placebo group, 1.4% in caffeine alone group. • One case of acute enteritis in patient who took ASA/acetaminophen/caffeine combination drug and one attack of ulcerative colitis in patient taking acetaminophen by itself from Diener (2005) RCT.	• Included in Derry (2014) meta-analysis. Reported separately because RCT has more detailed safety data. • Short-term exposure limited ability to find effects from chronic use. • Investigators judged whether adverse events were drug-related, but this judgment is subjective and is not presented in this table.

Table 4.4.2 (continued)

Lipton (1998) USA Bristol-Myers Squibb	2 tablets of ASA 250 mg/acetaminophen 250 mg/caffeine 65 mg vs. Placebo	Pain relief and safety	1,247 migraine patients	▪ No serious adverse effects. Severe adverse effects: 1.9% in drug-treated vs. 1.7% in placebo patients. ▪ Overall adverse events: 18% of drug-treated patients vs. 10.8% of placebo patients. ▪ Nausea signif higher in drug-treated than placebo patients (4.9% vs. 1.7%). Drug-treated patients also had dyspepsia and abdominal pain more often than placebo patients, but placebo patients had higher % with vomiting (1.6%) than drug-treated (0.2%). ▪ Overall: 8% GI symptoms in drug group vs. 4% GI symptoms in placebo group.	▪ RCT, double-blinded. Excluded patients with a history of vomiting during migraines due to lack of absorption of drugs. ▪ Placebo had similar appearance to active drug. ▪ Adverse events recorded in diary and elicited at clinical visits. ▪ Short-term, single-dose exposure limited ability to find effects from chronic use. ▪ Notable that lack of treatment led to vomiting, but treatment resulted in nausea.

Table 4.4.3 – Summary of Studies of Combination Acetaminophen-Antacid Products					
Randomized controlled clinical trials (RCTs)					
Author (Year)	**Exposure**	**Outcome**	**Cohort Size**	**Safety findings**	**Comments**
Burnett (2006) USA Sponsor: GlaxoSmithKline	acetaminophen+ sodium bicarb. (1,000 mg) vs. Placebo	Pain relief from sore throat	181 drug; 60 placebo	• No serious adverse events. • 11% of drug group vs. 5% of placebo group reported adverse events. • Most common adverse events: rhinitis and headache.	• Double-blind, randomized, placebo-controlled. Unclear if effervescent placebo was used. • Adult patients with sore throat. • Study lasted 6 hours; no post-dose follow-up, so limited window for adverse effects. • Mean age was 20 in both groups, so results not necessarily applicable to adults older than 25. • No signif. difference in adverse events. No serious adverse events. • Single-use: little likelihood of observing serious adverse events.
Moller (2000) Denmark Sponsor: Bristol-Myers Squibb	Efferv acetaminophen(1,000 mg) vs. acetaminophen, Efferv placebo, Tablet placebo	Dental pain relief	60 patients in each group except 62 in efferv placebo	• No serious adverse events. • Adverse events similar in each group; 104/242 patients (43%) reported adverse events. • Most common events: pain, headache, dry socket, surgery complication, post-op bleeding, post-op swelling.	• Double-blind, randomized, placebo-controlled. • Effervescent placebo was used. • Adults ages 18-50 after dental surgery. • 4-hour observation period; 1-week follow-up. Diaries for each patient. • Adverse events classified using WHO systems. • Single-use or two doses: little likelihood of observing serious adverse events. • Small numbers studied.
Nyström (1988)	Efferv	Dental	45 patients in	• No serious	• Double-blind,

Sweden Sponsor: Astra Alab AB	acetaminophen 500 mg or 1,000 mg vs. Diflunisil 500 mg	pain relief	500 mg efferv acetaminophen group, 46 in 1,000 mg efferv acetaminophen group, 41 in Diflunisil group	adverse events requiring medical treatment. • Adverse event numbers similar in each group. • Most common events: headache, nausea/vomiting, one post-op bleeding event.	randomized, controlled. • Effervescent placebo was used. • Adults after dental surgery. • Excluded 18/150 patients after entry to study, so bias is possible. • 10-hour observation period for each patient. • Single-use or two doses: little likelihood of observing serious adverse events. • Small numbers studied.

4.6 Appendix 5: Drug Safety Communication (6-6-16)

FDA Drug Safety Communications

FDA warns about serious bleeding risk with over-the-counter antacid products containing aspirin (Food and Drug Administration)

Safety Announcement

[06-06-2016] The U.S. Food and Drug Administration (FDA) is warning consumers about the risk of serious bleeding when using nonprescription, also known as over-the-counter or OTC, aspirin-containing antacid products to treat heartburn, sour stomach, acid indigestion, or upset stomach. Many other products for these conditions are available that do not contain aspirin.

These widely used products already contain warnings about this bleeding risk on their labels; however, we are continuing to receive reports of this serious safety issue. As a result, we will continue to evaluate this safety concern and plan to convene an advisory committee of external experts to provide input regarding whether additional FDA actions are needed.

OTC aspirin-antacid products are sold under various trade names, including Alka-Seltzer Original, Bromo Seltzer, Medique Medi Seltzer, Picot Plus Effervescent, Vida Mia Pain Relief, Winco Foods Effervescent Antacid and Pain Relief, and Zee-Seltzer Antacid and Pain Reliever. They are also available as generic products.

Consumers should always read the Drug Facts label carefully when purchasing or taking an OTC product to treat heartburn, acid indigestion, or sour or upset stomach. If the product contains aspirin, consider whether you should choose a product without aspirin to relieve your symptoms.

Aspirin is a commonly used pain reducer and fever reducer. It is a nonsteroidal anti-inflammatory drug (NSAID) that can increase the risk of bleeding, including in the stomach and gastrointestinal (GI) tract. Ask your pharmacist if you need help reading the Drug Facts label.

If you have one or more of the following risk factors, you may have a higher chance of serious bleeding when taking aspirin-containing antacid products:

- Are 60 years or older
- Have a history of stomach ulcers or bleeding problems
- Take a blood-thinning or steroid medicine
- Take other medicines containing NSAIDs such as ibuprofen or naproxen
- Drink three or more alcoholic drinks every day

Taking more of these medicines than the amount recommended or for a longer period than recommended will increase the risk of serious bleeding.

In 2009, a warning about the risk of serious bleeding was added to the labels of all OTC products that contain NSAIDs, including aspirin-containing antacid products. However, a search of the FDA Adverse Event Reporting System (FAERS) database identified eight cases of serious bleeding events associated with these products after the warning was added. All of these patients were hospitalized. Patients had underlying conditions such as the risk factors above that put them at greater risk for developing serious bleeding events (see Data Summary). The FAERS database includes only reports submitted to FDA so there are likely additional cases about which we are unaware.

We are continuing to evaluate this safety issue and will notify the public of the advisory committee meeting by posting notices in the Federal Register and on the FDA Advisory Committees web page and when we have additional information to share.

We urge consumers and health care professionals to report side effects involving OTC aspirin-containing antacid products or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Facts about Over-the-counter (OTC) Aspirin-containing Antacid Products

- These products combine an antacid (such as sodium bicarbonate or another antacid) that neutralizes stomach acid with aspirin, a nonsteroidal anti-inflammatory drug (NSAID).
- OTC aspirin-containing antacid products are widely used to treat heartburn, sour stomach, acid indigestion, or upset stomach, along with headache or body aches and pains.
- OTC aspirin-containing antacid products are sold under various trade names, including Alka-Seltzer Original, Bromo Seltzer, Medique Medi Seltzer, Picot Plus Effervescent, Vida Mia Pain Relief, Winco Foods Effervescent Antacid and Pain Relief, and Zee-Seltzer Antacid and Pain Reliever.

Additional Information for Consumers and Health Care Professionals

- Serious bleeding events have been reported with the use of over-the-counter (OTC) medicines that contain a combination of an antacid to treat heartburn, sour stomach, acid indigestion, or upset stomach, and the pain reliever aspirin.
- When purchasing or taking an OTC product to treat heartburn, acid indigestion, upset stomach, or sour stomach, always read the Drug Facts label carefully. If the product contains aspirin, consider whether that product is right for you, or if you could choose a product without aspirin to relieve your symptoms. Many OTC products are available that relieve heartburn and stomach symptoms but do not contain aspirin.
- If you have one or more of the following risk factors, you may have a higher chance of serious bleeding when taking aspirin-containing antacid products:
    - Are 60 years or older
    - Have a history of stomach ulcers or bleeding problems
    - Take a medicine to reduce the ability of your blood to clot. These are also known as anticoagulants or blood-thinning drugs. Some examples include warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, and heparin.
    - Take a steroid medicine to reduce inflammation. Some examples include prednisone, prednisolone, methylprednisolone, hydrocortisone, betamethasone, and dexamethasone.
    - Take other medicines containing nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen
    - Drink three or more alcoholic drinks every day
- Always read the Drug Facts labels included on antacids and all OTC medicines to find out if the product contains aspirin. Aspirin is an NSAID that can increase the risk of serious bleeding, including in the stomach, gastrointestinal (GI) tract, brain, and spinal cord.
- This serious bleeding can require hospitalization or the need for a blood transfusion.
- If you are not sure if a product contains aspirin, ask a pharmacist or your health care professional.
- Taking more of the medicine than the amount recommended or for a longer period than recommended will increase the risk of serious bleeding.
- If you are taking aspirin alone for your heart or for another reason, don’t stop taking it without first talking to your health care professional.
- Report side effects from OTC aspirin-containing antacid products or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page

Data Summary

A search of the FDA Adverse Event Reporting System (FAERS) database from January 1, 1969 (database initiation), through August 13, 2014, identified 41 cases of serious bleeding events reported with over-the-counter (OTC) products containing aspirin, sodium bicarbonate, and citric acid. All patients experienced serious outcomes resulting in hospitalization, and 21 patients required transfusions due to the blood loss. Most of the patients recovered. One death was

reported; however, the case provided few details of the patient's underlying medical conditions or the cause of death.

Of the 41 cases:

- 17 provided no details about the dosing
- 11 indicated the patient used the product routinely on a daily basis, ranging from once a day to six times a day or every 4 hours, which is within the recommended dosage
- Seven cases indicated the patient used the product as needed
- Three cases indicated the patient inappropriately used the product by taking more than the recommended maximum of eight tablets per day
- Three reported the patient used one dose of the product before developing the bleeding event
- For the 18 cases reporting a duration of use, the median time to onset of the bleeding event was 7.5 days (range of duration of use: a single day to 3 years)

The majority of patients using the aspirin-containing antacid products appeared to have had underlying conditions that put them at risk for developing serious bleeding events, particularly gastrointestinal bleeding events. Risk factors for developing bleeding were reported in 88% (36/41) of the cases, and included age greater than 60 years (n=23); use of anticoagulants, steroids, or nonsteroidal anti-inflammatory drugs (n=28); history of stomach ulcers (n=4); or history of alcohol abuse (n=5).