



# Reconsidering Caffeine: An Awake and Alert New Look at America's Most Commonly Consumed Drug

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RECONSIDERING CAFFEINE:

AN AWAKE AND ALERT NEW LOOK AT

AMERICA'S MOST COMMONLY CONSUMED DRUG

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ABSTRACT

*Caffeine is one of the most pervasively ingested addictive substances in the United States, yet astoundingly little attention is paid to its ubiquitous presence. This Paper examines caffeine, the substance, from many perspectives. First, it discusses caffeine with particular regard to its chemical properties; its presence in foods, beverages, and medications both naturally and as an additive; and its known impacts on human biological and psychological functioning. Relevant medical investigations of caffeine's therapeutic properties and its toxicology are included in order to better evaluate the benefits, the risks, and the relative safety of prolonged caffeine consumption. In light of more recent medical findings, the Paper finds that caffeine poses fewer serious health risks than previously thought, and the potential for damage to the vast majority of the consumer public is minimal.*

*The Paper also addresses issues of FDA regulation of caffeine, including a discussion of current regulation and classification of the substance both as a food product and as a drug product, as well as questioning the usefulness of greater consumer warning labels and promotion of improved public awareness of caffeine's various health effects. Due to both the paucity of long-term caffeine health studies and the conflicts among those studies, the Paper contends that heightened FDA regulatory scrutiny of American caffeine consumption is an unnecessary expenditure of limited resources. The Paper finds caffeine poses no material danger to the consumer, and dismisses the claims of prior authors to that effect as generally overstated. Finally, the Paper poses a hypothetical analysis of caffeine as both a new food additive and a new drug, in order to illustrate the FDA's modern regulatory process and demonstrate greater confidence in the safety of consumer caffeine use.*

## I. Introduction: Caffeine – The American Crutch

Picture this: a group of people are seated and quietly reading the morning newspaper in the nearby corner “Starbucks” coffee shop while sipping a “Grande Latte.”<sup>1</sup> Elsewhere, a team of frenetic business executives dash to the closest street vendor to grab a quick cup of black coffee or a “Diet Coke” to wake up for the next morning business meeting.<sup>2</sup> In dormitory rooms on college campuses everywhere, students sit staring at computer screens while drinking a wide variety of caffeinated beverages, or even ingesting OTC drugs like “Vivarin” to stay awake and finish the occasional all-night assignment.<sup>3</sup> In a quiet teahouse, people debate philosophy over a cup of Assam or Darjeeling black tea. Whether used as a day-starter, a work finisher, or a recreational excuse for conversation, substances containing caffeine have developed a certain contemporary cachet in American society, though they have been available for centuries.<sup>4</sup>

On the other hand, ever-increasing consumer vigilance regarding individual health causes many people to wonder about the addictive and potentially dangerous properties of caffeinated products. For a drug so commonly used, little attention is paid to the chemical itself, its abundant sources both in nature and in synthetics, the quantity of caffeine ingested on a daily basis, and the real effects of caffeine use (both short

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<sup>1</sup> “Starbucks” refers to the Starbucks Corporation, and “Grande Latte” is a proprietary designation.

<sup>2</sup> “Diet Coke” is a trademarked product of the Coca Cola Corporation.

<sup>3</sup> “Vivarin” is a trademarked over-the-counter caffeine pill.

<sup>4</sup> See Goodman & Gilman’s *THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*, NINTH EDITION, McGraw-Hill Health Professions Division (1996), at 672 (“The basis for the popularity of all the caffeine-containing beverages is the ancient belief that they have stimulant and antisoporific actions that elevate mood, decrease fatigue, and increase capacity for work. For example, legend credits the discovery of coffee to a prior of an Arabian convent. Shepherds reported that goats that had eaten the berries of the coffee plant gamboled and frisked about all through the night instead of sleeping. The prior, mindful of the long nights of prayer that he had to endure, instructed the shepherds to pick the berries so that he might make a beverage from them”). See also “Caffeine and Women’s Health,” INTERNATIONAL FOOD INFORMATION COUNCIL PUBLICATIONS (Aug. 2002), available at <http://ific.org/publications/brochures/caffwomenbroch.cfm>; (“As long ago as 2,700 B.C. the Chinese Emperor Shen Nung sipped hot brewed tea. Coffee’s origins date back to 575 A.D. when in Africa beans were used as money and consumed as food”).

and long term). These issues are now discussed in detail.

## II. Understanding Caffeine: The Drug and Its Effects

### A. Caffeine: The Chemical and its Sources

Caffeine is now thought to be “the most widely used psychoactive drug in the world.”<sup>5</sup> Some studies estimate that 90% or more of this country’s population uses caffeine, whether through foods, beverages, or prescription and over-the-counter medicines.<sup>6</sup> The most common sources of caffeine for Americans include brewed coffee, brewed tea, typical cola drinks, milk and dark chocolate, and over-the-counter medications like “Anacin” and “Vivarin.”<sup>7</sup>

Caffeine is an alkaloid, or nitrogen-containing substance, bearing the chemical formula  $C_8H_{10}N_4O_2$ .<sup>8</sup> It belongs to the family of chemicals known as methylxanthines, which also includes the closely related chemicals theophylline and theobromine.<sup>9</sup> In its pure form, caffeine “occurs as odorless, white, fleecy masses, glistening needles or powder.”<sup>10</sup> As with all methylxanthines, caffeine has low solubility and is therefore often combined with a wide variety of compounds to form complexes, such as the double salt sodium benzoate, for purposes

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<sup>5</sup>Goodman & Gilman, *supra* note 4 at 571. *See also* Prothro, *supra* note 5 at 66: (“Caffeine is one of the most widely used psychoactive substances in the United States and the world today”). *See generally* Jerome H. Jaffe, “Psychoactive Substance Use Disorders,” in COMPREHENSIVE TEXTBOOK OF PSYCHIATRY, 642, 683 (1989).

<sup>6</sup>*See* Brain, *supra* note 14.

<sup>7</sup>*See Id.*

<sup>8</sup>Prothro, Gwendolyn, “The Caffeine Conundrum: Caffeine Consumption and Regulation in the United States,” 27 CUMB. L. REV. 65, 66 (1996/1997).

<sup>9</sup>*See* “Wikipedia, the Free Encyclopedia – Caffeine,” *available at* <http://en.wikipedia.org/wiki/Caffeine>.

<sup>10</sup>*Id.*

of enhanced solubility in consumer goods like soft drinks.<sup>11</sup>

Caffeine and the other methylxanthines are found in nature “in plants widely distributed geographically.”<sup>12</sup> Tea, which is prepared from the leaves of the plant *Thea sinensis*, naturally contains all three of the aforementioned methylxanthines and is consumed by at least half of the entire world population.<sup>13</sup> Cocoa and chocolate are produced “from the seeds of *Theobroma cacao*”; both contain caffeine and theobromine, and both are used the world over.<sup>14</sup> The most obvious and important source of American caffeine intake, coffee, is produced from the *Coffea arabica* plant.<sup>15</sup> Prior to the deliberate insertion of additional caffeine during production, many sodas contain a natural form of caffeine “because of their content of extracts of the nuts of *Cola acuminata*.”<sup>16</sup> While it occurs abundantly in nature from a wide variety of sources, caffeine is also “created synthetically and by extraction from cocoa, coffee bean or tea leaf waste,” which allows for its inclusion in a greater variety of consumer products.<sup>17</sup>

#### B. Caffeine Dosages: Quantity in Consumer Products

It is difficult to arrive at a recommended ordinary consumption quantity, or a standard “dose,” since caffeine is present in various consumer goods at widely differing levels. Some sources suggest that one-hundred

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<sup>11</sup>Goodman & Gilman, *supra* note 4 at 673.

<sup>12</sup>*Id.* at 672.

<sup>13</sup>*Id.* (“*Thea sinensis*, a bush native to southern China and now extensively cultivated in other countries”).

<sup>14</sup>*Id.* A separate but relevant subject of study involves the combination and interaction effects of the methylxanthines as a group; since products like tea and cocoa contain multiple methylxanthines, an elevated (or perhaps conflicting) set of effects could be observed.

<sup>15</sup>*See Id.*

<sup>16</sup>*Id.* *See also* “What is Caffeine,” GLOSSARY OF FOOD RELATED TERMS, *available at* <http://ozans.4mg.com/glossary.htm>: (“Caffeine is a naturally-occurring substance found in the leaves, seeds or fruits of over 63 plant species worldwide”).

<sup>17</sup>*See* Prothro, *supra* note 5 at 66. *See also* Marshall Brain, “How Caffeine Works,” *available at* <http://health.howstuffworks.com/caffeine1.htm>: (“The chief source of pure caffeine is the process of decaffeinating coffee and tea”).

milligrams, whether delivered into the bloodstream by liquid or solid, is useful as a base-line single dosage.<sup>18</sup> Though caffeine content can differ markedly even within a product category, (for example, the amount of caffeine present in “real-world coffee” can range from seventy-five to two-hundred-fifty milligrams per serving), the rough quantity of caffeine in the most commonly ingested products is well known.<sup>19</sup>

A standard six ounce cup of drip-brewed coffee contains roughly one-hundred milligrams of caffeine, whereas a similarly sized cup of brewed tea contains roughly seventy milligrams.<sup>20</sup> Espresso, a common ingredient in many of today’s popular specialty coffee drinks, contains closer to one-hundred milligrams of caffeine per liquid ounce.<sup>21</sup> A conventional twelve ounce can of soda contains approximately fifty milligrams of caffeine, though specialty sodas such as “Jolt Cola” contain closer to seventy milligrams.<sup>22</sup> Milk chocolate contains roughly six milligrams of caffeine per ounce.<sup>23</sup> In the most common over-the-counter drugs, “Anacin” and “Excedrin” tablets contain thirty-two milligrams of caffeine each, while “Vivarin” contains two-hundred milligrams per tablet.<sup>24</sup>

More noteworthy than the specific quantity of caffeine in conventional consumer products is the quantity of each product ingested on a daily basis. While the customary six ounce cup of coffee may contain one-hundred milligrams of caffeine, the ordinary serving sizes of “Starbucks” coffees are twelve, sixteen, and twenty ounces each.<sup>25</sup> More than half of all adult Americans “drink an average of three and a half cups of coffee a day,

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<sup>18</sup> See “Wikipedia,” *supra* note 6.

<sup>19</sup> *Id.*

<sup>20</sup> Brain, *supra* note 14.

<sup>21</sup> “Wikipedia,” *supra* note 6.

<sup>22</sup> *Id.*

<sup>23</sup> See generally Brain, *supra* note 14.

<sup>24</sup> *Id.*

<sup>25</sup> Sizing information corresponds to the Starbucks Corporation’s usage of the terminology “Tall,” “Grande,” and “Venti,” which are twelve, sixteen, and twenty ounce sizes respectively.

in addition to tea, cola, chocolate and over-the-counter caffeine-containing drugs.”<sup>26</sup> If potential problems with adult caffeine consumption are an issue to be considered, the caffeine intake of children is even more important, because “the potency of caffeine on a human body depends on the body’s weight.”<sup>27</sup> Some sources suggest that “[t]he highest exposure to caffeine from soft drinks on a mg/ kg / day basis is among young children,” especially children under the age of six.<sup>28</sup>

### C. Caffeine Consumption I: Therapeutic Uses and Positive Mechanics

Since so many people are consuming so much caffeine on a daily basis, the short and long-term beneficial effects of such usage merit significant discussion.<sup>29</sup> Caffeine has a variety of pharmacological effects on organ systems and neural functions, “though the level and duration of the effect varies among bodies.”<sup>30</sup> It is absorbed into the bloodstream following ingestion via the lining of the stomach and the small intestine, and reaches peak levels in the circulation of the bloodstream between fifteen and forty-five minutes after consumption.<sup>31</sup> Caffeine stimulates the central nervous system, reaching its maximum effect between thirty and sixty minutes after absorption; this is accompanied by a temporary increase in metabolic function.<sup>32</sup> It also relaxes smooth muscle, particularly bronchial muscle, which accounts for its inclusion in a wide variety of asthma medications.<sup>33</sup>

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<sup>26</sup>Prothro, *supra* note 5 at 68. *Citing* Ed Blonz, “The Buzz About Caffeine,” *Better Homes and Gardens*, May 1995, at 50.

<sup>27</sup>*Id.* at 70.

<sup>28</sup>45 FED. REG. 69,817, 69,820 (1980). *Cited in* Prothro, *supra* note 5 at 68.

<sup>29</sup>*See* Brain, *supra* note 14: (“More than half of all American adults consume more than 300 milligrams (mg) of caffeine every day, making it America’s most popular drug by far”).

<sup>30</sup>Prothro, *supra* note 5 at 67.

<sup>31</sup>*See Id.*

<sup>32</sup>*Id.*

<sup>33</sup>Goodman & Gilman, *supra* note 4 at 677: (“Preparations are employed to relax bronchial smooth muscle in the treatment of asthma and to relieve dyspnea in the treatment of chronic obstructive pulmonary disease”).

Initially, caffeine's therapeutic application to small children was difficult; infants have incredible difficulty metabolizing caffeine until at least three to five months of age, while younger infants may be entirely unable to process it, and generally excrete it unchanged.<sup>34</sup> However, caffeine has found new popularity "in the treatment of the prolonged apnea that is sometimes observed in preterm infants."<sup>35</sup> Though the long-term effects of caffeine administration on infant growth and development are not entirely known, no negative correlations between infant development and caffeine use have been detected as yet.<sup>36</sup>

Caffeine has long been employed medically "as a mild diuretic," meaning it increases the body's ability to produce urine; this is precisely the rationale behind its inclusion in certain medications for menopausal women who are suffering from water retention.<sup>37</sup> Caffeine also acts as a stimulant for the cardiovascular system, though "[t]he actions of the methylxanthines on the circulatory system are complex and sometimes antagonistic, and the resulting effects largely depend on the conditions prevailing at the time of their administration."<sup>38</sup> Higher concentrations of caffeine have been known to produce tachycardia and other cardiac arrhythmias, but the risk of this in normal healthy individuals is minimal.<sup>39</sup>

These pharmacological effects last only as long as caffeine remains in the bloodstream; as time progresses following ingestion and absorption, the liver metabolizes the caffeine.<sup>40</sup> It is then excreted from the body through a number of channels, including urine, saliva, semen, and even breast milk.<sup>41</sup> While a number of fac-

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<sup>34</sup> See Alejandro Lopez-Ortiz, "Frequently Asked Questions About Coffee and Caffeine," available at <http://www.lib.ox.ac.uk/internet/news/faq/archive/caffeine-faq.html>. Cited in Prothro, *supra* note 5 at 67.

<sup>35</sup> Goodman & Gilman, *supra* note 4 at 677.

<sup>36</sup> See *Id.*

<sup>37</sup> Brain, *supra* note 14. See generally "Wikipedia," *supra* note 6. See also Goodman and Gilman, *supra* note 4 at 677: ("Caffeine, in probably subtherapeutic amounts, is incorporated into a number of over-the-counter preparations used for analgesia or to produce diuresis").

<sup>38</sup> See Goodman & Gilman, *supra* note 4 at 674: ("In addition to effects on the vagal and vasomotor centers in the brain stem, there is an array of more or less direct actions on vascular and cardiac tissues, in combination with indirect peripheral actions that are mediated by catecholamines and possibly by the rennin-angiotensin system. Therefore, the observation of a single function, for example, the blood pressure, is deceiving because the drugs may act on a variety of circulatory factors in such a way that the blood pressure may remain essentially unchanged").

<sup>39</sup> *Id.*

<sup>40</sup> See generally Goodman & Gilman, *supra* note 4.

<sup>41</sup> See Lopez-Ortiz, *supra* note 34.

tors, among which are pregnancy, liver disease, body weight, concurrent medications, and natural metabolic rate all influence the body's ability to break down caffeine, "its average half-life is three and one half hours," meaning that the average person will eliminate half of the amount of ingested caffeine within that time span.<sup>42</sup> Fortunately, caffeine is "quickly and completely removed from the brain and, unlike other central nervous system stimulants or alcohol, its effects are short lived."<sup>43</sup> Additionally, "caffeine does not affect concentration or higher mental functions, and hence caffeinated drinks are often consumed in the course of work."<sup>44</sup>

Put simply, people predominantly use caffeine to help them wake up in the morning, so that they will feel more alert and less tired. The chemical process behind this feeling of increased alertness, however, is actually quite complex, and requires a brief discussion of the body's sleep mechanics. In order for a person to fall asleep, adenosine is created in the brain, which then binds itself to specialized adenosine receptors.<sup>45</sup> This normal binding process causes drowsiness, through adenosine's slowing down of nerve cell activity.<sup>46</sup> Adenosine binding also simultaneously causes blood vessels in the body to dilate, presumably to increase the oxygen flow to and from the brain during the various stages of the sleep cycle.<sup>47</sup>

Caffeine interferes with the body's natural tendencies to feel tired and sleep by engaging in adenosine replacement; to a nerve cell, caffeine's xanthine structure appears similar to adenosine, allowing the substituted

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<sup>42</sup>Prothro, *supra* note 5 at 67. *See also* Lopez-Ortiz, *supra* note 34; the half-life of caffeine in the body of a pregnant woman can be as much as eighteen to twenty hours, while caffeine ingested concurrently with nicotine produces faster metabolism and a shorter half-life of three hours or so.

<sup>43</sup>"Wikipedia," *supra* note 6.

<sup>44</sup>*Id.*

<sup>45</sup>*See generally* Goodman & Gilman, *supra* note 4.

<sup>46</sup>*See generally* Brain, *supra* note 14.

<sup>47</sup>*See Id.*

binding process to occur.<sup>48</sup> However, caffeine chemically stimulates nerve cell activity rather than slowing it down, causing the familiar feeling of “lift.”<sup>49</sup> Caffeine also causes the constriction of cranial blood vessels in lieu of the dilation caused by adenosine; this is precisely the rationale for its inclusion in a variety of over-the-counter pain relievers.<sup>50</sup> “Pain relievers that contain caffeine appear to provide somewhat more relief than caffeine-free products.”<sup>51</sup>

Once caffeine has caused the brain’s neuron firing to increase rather than decrease, the pituitary gland stimulates the adrenal gland’s release of epinephrine (adrenaline) in response to the increased activity.<sup>52</sup> Therefore, many of the “lifting” effects felt after ingesting a caffeinated substance are actually secondary central nervous system effects stemming from the body’s increased adrenaline production; dilated pupils, increased respiratory capacity, elevated heart rate, and muscle tightening are all natural results of the release of adrenaline.<sup>53</sup> It is noteworthy that the body’s adrenaline production following significant caffeine intake is much like an emergency “fight or flight” response to a crisis; the body is able to generate improved short-term mental and physical performance largely due to its being “fooled” into a state of emergency.<sup>54</sup>

The interaction between caffeine and dopamine is perhaps more important, and helps to explain caffeine’s addictive nature. Dopamine is a neurotransmitter that activates the brain’s pleasure center.<sup>55</sup> As with amphetamines, caffeine absorption causes a reduction in the rate of dopamine reuptake, increasing the

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<sup>48</sup> *See Id.*

<sup>49</sup> Brain, *supra* note 14.

<sup>50</sup> *See Id.* (“You can see that caffeine also causes the brain’s blood vessels to constrict, because it blocks adenosine’s ability to open them up. This effect is why some headache medicines like Anacin contain caffeine - if you have a vascular headache, the caffeine will close down the blood vessels and relieve it”). In other words, caffeine reduces intracranial pressure to relieve vascular headaches.

<sup>51</sup> “Caffeine in Pain Relievers,” Consumer Rep. on Health, July 1995, at 76.

<sup>52</sup> *See* Brain, *supra* note 14.

<sup>53</sup> *See Id.* *See also* Goodman & Gilman, *supra* note 4 at 674: (“Persons ingesting caffeine or caffeine-containing beverages usually experience less drowsiness, less fatigue, and a more rapid and clearer flow of thought. . . . As the dose of caffeine or theophylline is increased, signs of progressive CNS stimulation are produced. . .”).

<sup>54</sup> *See Id.*

<sup>55</sup> Brain, *supra* note 14.

body's overall dopamine level.<sup>56</sup> Though the effects are much milder with caffeine than with amphetamines or strong narcotics like cocaine and heroin, the dopamine reuptake inhibiting mechanism is thought to be much the same.<sup>57</sup> This contributes to caffeine's addictiveness; as the body receives neural signals indicating pleasure from the intake of caffeine, it wants to maintain these mildly pleasurable feelings.<sup>58</sup>

#### D. Caffeine Consumption II: Addiction

The primary complaint of most consumers against caffeine is addictiveness. In the context of adrenaline and dopamine production, caffeine causes the body to experience artificial sensations of lift and pleasure.<sup>59</sup> In the short-term, the body benefits from caffeine as it "restores mental alertness or wakefulness during fatigue or drowsiness," and helps the body remain active when rest is not an option.<sup>60</sup> However, the levels of adrenaline and dopamine in the body are both diminished as the majority of the substance is metabolized, leading to fatigue and depression, and a greater desire to have another dose instead of experiencing a mood crash.<sup>61</sup> In the long-run, therefore, caffeine consumption can be a difficult cycle to break, especially when considering its short-term benefits.<sup>62</sup>

The FDA has previously noted that "chronic ingestion of caffeine in larger than recommended doses can lead to 'habituation,' which is a mild form of addiction."<sup>63</sup> Though significantly milder and less damaging in effect than other related forms of addiction, recurrent caffeine use can cause psychological dependence in the user.<sup>64</sup> Physical and psychological dependence are marked by several characteristics, including "tolerance,

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<sup>56</sup> *Id.*

<sup>57</sup> *Id.*

<sup>58</sup> *See Id.*

<sup>59</sup> *Id.* *See generally* Goodman & Gilman, *supra* note 4.

<sup>60</sup> *See* Kathleen Doheny, "Smell the Coffee – Just Don't Drink Too Much," L.A. Times, Jan. 9, 1996, at E1.

<sup>61</sup> *See generally* Brain, *supra* note 14.

<sup>62</sup> Brain, *supra* note 14.

<sup>63</sup> 53 FED. REG. 6100, 6103 (1988).

<sup>64</sup> *See* "Wikipedia," *supra* note 6. *See also* Eric C. Strain, et al., "Caffeine Dependence Syndrome: Evidence from Case Histories and Experimental Evaluations," 272 JAMA 1043 (1994): ("caffeine exhibits the features of a typical psychoactive

withdrawal, persistent desire, or unsuccessful attempts to reduce consumption and persistent use despite adverse psychological or physical consequences.”<sup>65</sup>

Tolerance and withdrawal are the most commonly reported indicators of caffeine habituation, and can take place after ceasing to consume daily dosages of two-hundred-fifty milligrams or less.<sup>66</sup> Tolerance can occur rapidly based on the stimulant properties of caffeine, suggesting that mild withdrawal symptoms may occur even if caffeine has only been ingested for a short period of time.<sup>67</sup> Withdrawal symptoms can include “throbbing headaches, drowsiness, nausea, lethargy, irritability, nervousness, and depression,” and the onset of these symptoms can be as early as eighteen hours after the last intake.<sup>68</sup> A withdrawal headache, commonly called a “caffeine headache,” is actually indicative of a hypersensitivity to adenosine; the sensitivity causes a decline in blood pressure, an opening of the brain’s blood vessels, and increased intracranial pressure leading to some sensations of pain and throbbing.<sup>69</sup> Individuals wishing to reduce their caffeine dependency are better off doing so by gradually reducing their daily intake, as withdrawal symptoms are diminished by a gradual step-down.<sup>70</sup>

Though habituation in any form arguably poses some risk, the negative effects of caffeine are widely disputed; the available caffeine literature is marked by a continual disagreement among sources regarding the potential long-term addictiveness (and therefore dangerousness) of the drug.<sup>71</sup> While some sources contend that

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substance of dependence”).

<sup>65</sup> See Wallace B. Pickworth, “Caffeine Dependence,” *Lancet*, Apr. 29, 1995, at 1066, *cited in* Prothro, *supra* note 5 at 73.

<sup>66</sup> Doheny, *supra* note 60.

<sup>67</sup> Goodman & Gilman, *supra* note 4 at 572.

<sup>68</sup> See Prothro, *supra* note 5 at 73. *But see* Goodman & Gilman, *supra* note 4 at 572: (“Although a withdrawal syndrome can be demonstrated, few caffeine users report loss of control of caffeine intake or significant difficulty in reducing or stopping caffeine, if desired”).

<sup>69</sup> See “Wikipedia,” *supra* note 6.

<sup>70</sup> See Doheny, *supra* note 60.

<sup>71</sup> A notable discrepancy between sources exists when discussing the severity of caffeine’s addictiveness, particularly with

caffeine can be a serious and compelling addiction, the American Psychiatric Association disagrees to the extent that it has omitted caffeine from its listing of addicting stimulants.<sup>72</sup> In a letter from the National Soft Drink Association, the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION article entitled “Caffeine Dependence Syndrome” was heavily criticized for its conclusions regarding dependency.<sup>73</sup> The letter disputes the accuracy of the study based on its sample population, but more importantly distinguishes caffeine use from other addictions because “steadily increasing doses are not associated with caffeine ingestion.”<sup>74</sup> Since caffeine is at least mildly addictive and has some potential for unpleasant withdrawal effects, consumers should be aware and exercise greater vigilance before consuming caffeinated products.

#### E. Caffeine Consumption III: Other Possible Toxicology

Irrespective of its remedial properties and its potential to cause habituation, caffeine is still poisonous given a large enough dosage. Though fatalities from caffeine use are rare, they have occurred in the past; sixteen fatalities were attributed to caffeine toxicity in the period between 1959 and 1987.<sup>75</sup> The LD<sub>50</sub>, or “lethal dose fifty percent,” is the basis of all toxicological measurement.<sup>76</sup> It refers to the quantity of a particular substance that kills fifty percent of a sample population, and is colloquially known as the “semi-lethal dose.”<sup>77</sup> Caffeine’s LD<sub>50</sub> is ten grams; put in terms of six ounce cups of coffee (each containing an estimated one-hundred milligrams of caffeine), fatality may result if approximately one-hundred cups of coffee are ingested within a very short period of time.<sup>78</sup>

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regard to frequency and severity of withdrawal symptoms following cessation of caffeine intake. Based on the descriptions of caffeine’s medical effects in Goodman & Gilman, it is a reasonable conclusion that the known dangers of caffeine have been overstated in numerous other sources.

<sup>72</sup>See Goodman & Gilman, *supra* note 4 at 572: (“Thus caffeine is not listed in the category of addicting stimulants”), *citing* a 1994 APA report.

<sup>73</sup>Richard H. Adamson & Howard R. Roberts, “Letter: Caffeine Dependence Syndrome,” 273 JAMA 1418 (1995). The potential bias of this source is considerable, though the points raised against the previous study are noteworthy.

<sup>74</sup>See *Id.*

<sup>75</sup>See Prothro, *supra* note 5 at 69.

<sup>76</sup>See “Wikipedia, the Free Encyclopedia – LD<sub>50</sub>,” *available at* <http://en.wikipedia.org/wiki/LD50>.

<sup>77</sup>See *Id.*

<sup>78</sup>See Prothro, *supra* note 5 at 69. See also “Wikipedia,” *supra* note 6.

This type of fatality is extremely unlikely. Besides the fact that enormous quantities of caffeine are required to reach fatal toxic levels, and such quantities must be ingested rapidly, the most commonly used caffeine-containing substances such as coffee and soda would cause significant gastric irritation, acid secretion, nausea, and vomiting, irrespective of their caffeine content if ingested at those volumes.<sup>79</sup> More importantly, these effects would likely take place long before the fatal toxicity could be reached.<sup>80</sup>

Even in non-lethal doses, large quantities of caffeine can cause potentially significant health problems, including conditions that may be considered “long-term poisoning.”<sup>81</sup> According to an article in the JOURNAL OF FORENSIC SCIENCE, a one-thousand milligram dose of caffeine, or one-tenth of the LD<sub>50</sub>, has been known to cause convulsions, uncomfortably rapid breathing, tachycardia, hyperglycemia, and ketonuria.<sup>82</sup> Continual caffeine intake at lower levels can also cause borderline toxic responses – restlessness, disturbed sleep, irritability, muscle tension, cardiac arrhythmia, persistent nervousness, or sporadic reactions similar to anxiety attacks.<sup>83</sup>

Incidences of significant or borderline toxic responses to caffeine are not frequent enough to be considered problematic<sup>84</sup>; however, there are “rare persons who are so sensitive to caffeine that even a single cup of coffee will cause a response bordering on the toxic.”<sup>85</sup> Certain groups are also more generally susceptible to the effects of caffeine; because of its correlation with body weight, children are often disproportionately

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<sup>79</sup>See Goodman & Gilman, *supra* note 4 at 678.

<sup>80</sup>See *Id.*: (“It has been long known <and perhaps forgotten> that beverages made from roasted grain containing no caffeine stimulate acid secretion in human beings as much as does coffee. Decaffeinated coffee is only slightly less potent than the natural product in enhancing the secretion of gastrin and acid, and both are about twice as effective as is an equivalent amount of caffeine”).

<sup>81</sup>See *Id.*: (“Overindulgence in xanthine beverages may lead to a condition that might be considered one of long-term poisoning”).

<sup>82</sup>P.L. Morrow, “Caffeine Toxicity: A Case of Child Abuse by Drug Ingestion,” 32 J. FORENSIC SCI. 1801, 1803 (1987).

<sup>83</sup>See Prothro, *supra* note 5 at 70. See generally Brain, *supra* note 14. See generally Goodman & Gilman, *supra* note 4.

<sup>84</sup>See generally “Caffeine Health – What to Worry About,” available at <http://www.coffeeforums.com>.

<sup>85</sup>See Goodman & Gilman, *supra* note 4 at 678.

affected by smaller doses of caffeine.<sup>86</sup> Similarly, some elderly people have been known to experience a disproportionate interruption of the sleep cycle simply from ingesting caffeinated medications.<sup>87</sup>

Pregnant women are also generally advised to avoid caffeine, for a variety of reasons. Though it has not been linked to “pre-term labor, low birth weight, or birth defects,” physicians generally suggest that pregnant women abstain from caffeine intake due to the suspicion of an increased likelihood for miscarriage and intra-uterine growth retardation.<sup>88</sup> Because of the potential for caffeine transmission through breast milk, women who are planning to breast feed a child are similarly encouraged to avoid caffeine.<sup>89</sup>

Sleep deprivation caused by caffeine is worthy of separate mention. While the obvious “wake up” benefit of a morning cup of coffee is well known, the cost associated with this benefit is the potential for delayed negative effect on adenosine absorption.<sup>90</sup> Adenosine is critical to deep, restful sleep; the later in the day an individual

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<sup>86</sup>Prothro, *supra* note 5 at 70: (“And children often display symptoms of attention deficit / hyperactivity disorder when they consume caffeine. . . . Because the potency of caffeine on a human body depends on the body’s weight, children are far more sensitive to caffeine than adults – a single soft drink <containing 30-46 mg of caffeine> affects a young child the way two cups of coffee <130-230 mg of caffeine> affect an adult”).

<sup>87</sup>*Id.*

<sup>88</sup>*Id.*, citing Isabel Fortier et al., “Relation of Caffeine Intake During Pregnancy to Intrauterine Growth Retardation and Preterm Birth,” 137 AM. J. EPIDEMIOLOGY 931, 931-40 (1993).

<sup>89</sup>*Id.* According to some sources, caffeine may correlate with greater difficulty among women in conceiving children, though further exploration of this linkage is required; *See e.g.* Doheny, *supra* note 60. *But see* “Caffeine CERHR Study,” (Aug. 2003), available at <http://cerhr.niehs.nih.gov/genpub/topics/caffeine-ccae.html>, stating that (“numerous studies have examined the effects of caffeine intake on fertility and pregnancy. Most studies found that moderate caffeine intake does not affect fertility or increase the chance of having a miscarriage or a baby with birth defects; some studies did find a relationship between caffeine intake and fertility or miscarriages. However, most of those studies were judged to be inadequate because they did not consider other lifestyle factors that could contribute to infertility or miscarriages. The Organization of Teratology Information Services (OTIS) stated that there is no evidence that caffeine causes birth defects in humans. Groups such as OTIS and Motherisk agree that low caffeine intake (<150 mg/day or 1-1/2 cups of coffee) will not likely increase a woman’s chance of having a miscarriage or a low birth weight baby. Motherisk recommends that caffeine intake by pregnant women not exceed 150 mg/day whereas OTIS stated that moderate caffeine intake of 300 mg/day (equivalent to about 3 cups of coffee) does not seem to reduce fertility in women or increase the chances of having a child with birth defects or other problems. Caffeine can enter breast milk, and high amounts can cause the baby to become wakeful and agitated. The American Academy of Pediatrics recommends that nursing women limit caffeine intake, but states that no harm is likely to occur in a nursing child whose mother drinks one cup of coffee a day. OTIS recommends that pregnant and nursing women drink plenty of water, milk, and juice and not substitute those fluids with caffeinated beverages”).

<sup>90</sup>*See* Brain, *supra* note 14.

consumes caffeine, the longer the adenosine replacement will take place and conflict with ordinary restful sleep cycles.<sup>91</sup> For example, using caffeine's estimated three and a half hour half-life, a single one-hundred milligram dose of the drug taken at four o'clock p.m. will be at half strength at seven thirty. In general, more caffeine consumed later in the day will be increasingly likely to cause sleep disturbances; this further fuels the need for caffeine to facilitate the body's awakening the following morning.<sup>92</sup>

Caffeine also poses a potential problem when considered in concert with other prescription drug therapies and physician diagnoses. Goodman & Gilman's chapter on methylxanthines notes

the xanthine beverages present a medical problem in that a large fraction of the population consumes enough caffeine to produce substantial effects on a number of organ systems. Hence, the physician should give due consideration to the possible contribution of caffeine to the presenting signs and symptoms of patients, as well as to its potential interaction with any contemplated therapeutic regimen.<sup>93</sup>

Considering its known stimulating effects, those patients who could frustrate existing medical conditions through its use should avoid caffeine intake. For example, people with abnormal heart function, including tachycardia and arrhythmia, should avoid caffeine because it could unnecessarily stimulate cardiac function.<sup>94</sup> Similarly, people with existing sleep disorders should avoid the interruptive effects of adenosine replacement. Finally, patients with gastrointestinal dysfunction of any kind, including gastro-esophageal reflux disease and peptic ulcers, should limit intake or omit caffeine entirely from daily consumption.<sup>95</sup>

#### F. Caffeine: The Problem of Disputed Science

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<sup>91</sup> *See Id.*

<sup>92</sup> *See Id.*

<sup>94</sup> *See Prothro, supra note 5 at 71.*

<sup>95</sup> *See generally Goodman & Gilman, supra note 4.*

Though caffeine is generally considered to be a safe product provided it is taken in small quantities, it may still be considered a poisonous substance regardless of the amount ingested.<sup>96</sup> Some sources are more concerned about its ready availability to the public, fearing untold long-term risk of overuse.<sup>97</sup> Many sources, however, defend the use of caffeine, claiming that much of the previous study research implicating it in a variety of health problems was poorly done or at best inconclusive.<sup>98</sup>

Several of the presumed linkages between caffeine use and significant health problems have recently been debunked as a result of new laboratory information.<sup>99</sup> For example, a famous 1980 study posited a link between caffeine use and fibrocystic breast disease; the correlation was later summarily dismissed.<sup>100</sup>

The supposed connection was suggested by a surgeon's study, in 1980, which relied on interviews with a small number of women but included no objective examination of their breast tissue. Since then, the few well-designed studies have found no association.<sup>101</sup>

Medical studies of caffeine continue to evolve and conflict; this makes definitive causal connections between caffeine and individual health concerns increasingly more difficult to establish.

A clear example of the conflicts among caffeine data involves the perceived correlation between caffeine use and bone fragility, particularly in post-menopausal women. According to an older Harvard-based study of more than one-hundred-thousand nurses, caffeine intake has a negative correlation with the body's ability to retain calcium, potentially altering bone density and increasing the likelihood of bone fracture and osteoporosis.<sup>102</sup> However, a recent evaluation of bone density data refutes the presumed linkage between caffeine use and calcium retention, and suggests that there is no verifiable independent link between bone fragility

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<sup>96</sup> See "Caffeine Health," *supra* note 84.

<sup>97</sup> See Prothro, *supra* note 5 at 71.

<sup>98</sup> See generally Adamson & Roberts, *supra* note 73.

<sup>99</sup> See generally "Caffeine Health," *supra* note 84.

<sup>100</sup> See "Questions and Answers; Caffeine and Breast Disease," CONSUMER REP., July 1995, at 493.

<sup>102</sup> Jane Brody, "Caffeine, The Doctor's Report," Dallas Morning News, Sept. 25, 1995, at 3C.

and the use of caffeine-containing substances.<sup>103</sup> Therefore significant concern about the issue is thought to be unfounded.<sup>104</sup>

Elevated risk of heart disease is a second important example of conflicting data in caffeine studies, especially since heart disease is now the largest cause of death in the United States.<sup>105</sup> While “some studies linked caffeine consumption to an increased risk of heart disease, particularly in men,”<sup>106</sup> more recent research reflects no such negative correlation between caffeine intake and heart disease.<sup>107</sup>

Cardiovascular disease (CVD)...has been the subject of extensive medical and scientific research for several decades. While researchers have differed in their conclusions over time, new evidence in 1999 strongly indicates that consumption of coffee and caffeine does not contribute to CVD, finding neither caffeinated nor decaffeinated coffee associated with the risk of stroke – even for those drinking more than four cups of coffee a day.<sup>108</sup>

A 1994 review of the relevant medical literature similarly concluded that, “[t]he largest and better studies suggest that coffee is not a major risk factor for coronary disease.”<sup>109</sup> Numerous other studies reflecting similar findings have been done in the past fifteen years, indicating that the espoused link between caffeine consumption and heart disease is probably spurious.<sup>110</sup>

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<sup>103</sup>See “Coffee, Caffeine, and Osteoporosis,” The Coffee Science Information Centre, *available at* <http://www.cosic.org/mainissues/article/11>: (“Earlier papers have suggested that caffeine may affect bone health, though these researchers stress that uncontrolled confounding factors may be responsible. The vast majority of recently published studies do not suggest caffeine as an independent risk factor for osteoporosis”).

<sup>104</sup>See *Id.*

<sup>105</sup>See “Understanding Coffee, Caffeine, and Cardiovascular Disease,” Coffee Science Source, *available at* <http://www.coffeescience.org/heart.html>: (“Cardiovascular disease (CVD), coronary heart disease, is the number one cause of death in America”).

<sup>106</sup>Prothro, *supra* note 5, *citing* Dag S. Thelle et al., “Does Coffee Raise Serum Cholesterol Level,” 308 NEW ENG. J. MED. 1454-57 (1983); Andrea Z. LaCroix et al., “Coffee Consumption and the Incidence of Coronary Heart Disease,” 315 NEW ENG. J. MED. 977-82 (1986); Lynn Rosenberg et al., “Coffee Drinking and Nonfatal Myocardial Infarction in Men Under 55 Years of Age,” 128 AM. J. EPIDEMIOLOGY 570-78 (1988); Lynn Rosenberg et al., “Coffee Drinking and Nonfatal Myocardial Infarction in Young Women: An Update,” 126 AM. J. EPIDEMIOLOGY 147-49 (1987).

<sup>107</sup>See “Understanding Coffee, Caffeine, and Cardiovascular Disease,” *supra* note 105.

<sup>109</sup>See Warren G. Thompson, “Coffee: Brew or Bane?” 308 AM. J. MED. SCI. 349, 349-57 (1994).

<sup>110</sup>See *e.g.* Walter C. Willet et al., “Coffee Consumption and Coronary Heart Disease in Women,” 275 JAMA 458, 458-62

At one time, caffeine was erroneously thought to be potentially carcinogenic; due to its diuretic properties, caffeine was believed to be linked to increased likelihood of bladder cancer.<sup>111</sup> However, a new wealth of study data now not only suggests that caffeine has no links to the promotion of cancer growths, the data also shows that caffeine-containing substances may actually combat certain types of cancer formation.<sup>112</sup> Though more information is needed to link caffeine to combating cancer, sufficient data exists to remove caffeine from consideration as a carcinogen.<sup>113</sup>

Several other presumed health linkages of lesser severity have also recently been called into question. For example, caffeine intake was once thought to be highly correlated with spikes in blood pressure, elevated serum cholesterol levels, and the exacerbation of existing cardiac conditions, including arrhythmia.<sup>114</sup> New

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(1996); utilizing a data set including 85,000 women over a ten year period, and adjusting for known risk factor variables, the authors found no link whatsoever between risk of coronary heart disease and coffee consumption in women, even for women ingesting more than six cups of coffee daily. *See also* Diederick E. Grobbee et al., “Coffee, Caffeine and Cardiovascular Disease in Men,” 323 *NEW ENG. J. MED.* 1026, 1026-32 (1990); finding no link between heart disease and caffeine consumption in a sample of over 45,000 men, whose daily caffeine intake included four or more cups of coffee.

<sup>111</sup>*See e.g.* Jean Carper, “Caffeine: The Bitter Truth,” *USA Weekend Magazine*, available at [http://www.usaweekend.com/99\\_issues/991003/991003eatsmart.html](http://www.usaweekend.com/99_issues/991003/991003eatsmart.html): (“[t]here’s little evidence that caffeine promotes cancer, except possibly bladder cancer”).

<sup>112</sup>*See e.g.* “Other Questions About Coffee and Health – Coffee and Caffeine Content,” available at <http://www.coffeescience.org/other.html>: (“Decades of research and centuries of human consumption confirm the safety of coffee and caffeine. . . . In fact, recent scientific research carried out at the Mayo Clinic, Harvard School of Public Health, U.S. Veterans Administration and other medical centers show that coffee is not only safe but beneficial – drinking from 2 to 4 cups of coffee a day may lower the risk of colon cancer (25%), gallstones (45%), cirrhosis of the liver (80%), and Parkinson’s Disease (50-80%), among other diseases”). *See also* Giovannucci, “Meta-Analysis of Coffee Consumption and Risk of Colorectal Cancer,” 147 *AM. J. EPIDEMIOLOGY* 1043, 1043-1052 (June 1998); consolidating seventeen separate studies on colorectal cancer and caffeine consumption, and finding a 24% reduced risk among consumers of four or more cups of coffee per day. *See also* “Caffeine Clue to Fighting Cancer,” *BBC News World Edition*, available at <http://news.bbc.co.uk/2/hi/health/2207153.stm>; discussing a University College London study which found that: (“Chocolate, cola and coffee could form the basis of new anti-cancer drugs, scientists believe. Researchers in the UK have found that caffeine and theophylline may be effective in fighting cancer tumours [sic]”). *See also* Carper, *supra* note 111: (“Recent Japanese research suggests that caffeine alters hormones in ways that may reduce the odds of breast cancer. New research in Switzerland has found coffee drinkers have a 27% lower risk of developing colon cancer. A study at Harvard suggested four to five cups of coffee a day reduced the risk of colorectal cancer by 24%”).

<sup>113</sup>*See* “Coffee, Caffeine, and Cancer,” *The Coffee Science Information Centre*, available at <http://www.cosic.org/mainissues/article/14/>: (“In 1990, IARC, the International Agency for Research on Cancer held a monograph on Coffee, Caffeine, Tea, and Mate. . . . Coffee was cleared in all areas with the exception of bladder cancer where there was insufficient evidence available at that time. Several studies since have clearly shown no linkage between coffee consumption and bladder cancer”). *See also* “Food, Nutrition and the Prevention of Cancer: A Global Perspective,” *American Institute for Cancer Research*, (1997): (“Most evidence suggests that regular consumption of coffee and/or tea has no significant relationship with the risk of cancer at any site”).

<sup>114</sup>*See* “Understanding Coffee, Caffeine, and Cardiovascular Disease,” *supra* note 105.

data suggests that each of these health linkages is suspect. For instance, while caffeine certainly does correlate to a short-term spike in blood pressure to a xanthine-naïve body, such effect is “transient,” and “[n]o changes in blood pressure appear to occur in regular users of caffeine.”<sup>115</sup> Furthermore, serum lipid and cholesterol levels do not show any increase in coffee prepared “by drip machines and percolators.”<sup>116</sup>

Admittedly, physicians generally remain cautious and encourage patients suffering from mild cardiac dysfunction to avoid excessive caffeine intake; there is little incentive not to follow this precautionary measure.<sup>117</sup> However, a 1991 article reviewing medical studies on coffee and caffeine in conjunction with arrhythmias and tachycardia found that a daily dose of five-hundred milligrams of caffeine, or the rough equivalent of five standard cups of coffee, “does not increase the frequency or severity of cardiac arrhythmias or ventricular tachycardia in healthy people or those with CVD.”<sup>118</sup> Thus, even health problems once considered to be obviously correlated with caffeine use are now being substantially called into question, or dismissed entirely.

#### G. Caffeine Alternatives: Balancing Costs and Benefits

The long-popular American slogan, “everything in moderation,” applies just as well to caffeine as it does to almost any other food, drug, or activity. In very large doses, caffeine is admittedly a poison. In small doses and in rare circumstances, caffeine can potentially cause health problems, though the scope of these problems and the level of medical concern both continue to change with new research developments. This

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<sup>115</sup>See *Id.*, citing Annette Bak and Diederick Grobbee, “Caffeine, Blood Pressure and Serum Lipids,” 53 AM. J. CLINICAL NUTRITION 971, 971-974 (1991).

<sup>116</sup>*Id.*, referring to a Scandinavian study that found small increases in serum lipids only through preparation of unfiltered boiled coffee – (“a process little used in the U.S.”).

<sup>117</sup>See generally Goodman & Gilman, *supra* note 4.

<sup>118</sup>See *Id.*, citing M. G. Meyers, “Caffeine and Cardiac Arrhythmias,” 114 ANNALS OF INTERNAL MED. 147, 147-150 (1991).

is, practically speaking, no different from any other food or drug item in daily life; too much of virtually anything can be toxic. However, even considering its addictiveness, caffeine is seemingly harmless the vast majority of the time, for the vast majority of people concerned.<sup>119</sup>

Even still, the market has produced alternatives to, and substitutes for, caffeine. In the early 1980s, after the market produced a “health craze,” soda companies began producing numerous decaffeinated colas; these sodas continue to be widely available today.<sup>120</sup> Nowadays, decaffeinated options are made available for consumers virtually everywhere teas and coffees are sold. For those consumers concerned with caffeine content in over-the-counter pain relievers, numerous replacement drugs do not have caffeine as an ingredient.<sup>121</sup>

One particular new source of concern is the American public’s recent infatuation with herbal remedies and supplements; many stimulants, including Ma Huang (*Ephedra sinensis*), Ginseng (*Panax quinquefolium*), and Guarana (*Paullinia cupana*), have become exceedingly common in the market, both as over-the-counter supplements and in food and beverage products, particularly energy drinks.<sup>122</sup> Besides the short and long-term health effects specific to each natural substance, some products like Ma Huang are variations of Ephedrine (recently pulled from the market by the FDA),<sup>123</sup> and others contain large quantities of caffeine and synthetic caffeine substitutes.<sup>124</sup>

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<sup>119</sup>See generally Thompson, *supra* note 109. See generally Goodman & Gilman, *supra* note 4.

<sup>120</sup>See Prothro, *supra* note 5 at 74, citing Toni Minarich & Janet Havter, “Elephantine Enlightenment,” Beverage World, July 1995, at 66.

<sup>121</sup>See e.g. “Anacin” and “Excedrin” versus other common pain relievers such as ibuprofen.

<sup>122</sup>A search, available at <http://www.google.com>, for the combined terms “Buy”, “Ginseng”, “Guarana”, and “Ma Huang” yielded more than seven thousand web pages, the vast majority of which were purchasing sites.

<sup>123</sup>See “Sales of Supplements Containing Ephedrine Alkaloids (Ephedra) Prohibited,” available at <http://www.fda.gov/oc/initiatives/ephedra/february2004/>: (“On April 12, 2004, a final rule went into effect prohibiting the sale of dietary supplements containing ephedrine alkaloids <ephedra>. Ephedra, also called Ma Huang, is a naturally occurring substance derived from plants. Its principal active ingredient is ephedrine, which when chemically synthesized is regulated as a drug. In recent years ephedra products have been extensively promoted to aid weight loss, enhance sports performance, and increase energy. But FDA has determined that ephedra presents an unreasonable risk of illness or injury. It has been linked to significant adverse health effects, including heart attack and stroke”).

<sup>124</sup>See e.g. “Body and Fitness,” available at <http://www.bodyandfitness.com/products/health/energy.htm>; one particular proprietary energy supplement sold at this source, a capsule called “Super Enermax,” contains the following ingredients: 200mg guarana, 200mg yerba mate, 100mg green tea, 50mg ginseng, 50mg kola extract, and 50mg rhodiola. Most of these additives contain some portion of natural caffeine, particularly guarana (half of the 200mg is caffeine), and yerba mate (a dried herb containing even higher levels of natural caffeine). Therefore, though the product may contain a wide variety of “natural energy-

The FDA faces a separate regulatory challenge in dealing with these products, many of which do not present the natural caffeine content of the product's ingredients for greater consumer awareness.<sup>125</sup> Fortunately, due to much of the recent study data's suggestion that caffeine is not nearly as dangerous as once thought,<sup>126</sup> the proliferation of caffeinated substances in the marketplace is not of great concern; individual consumers can readily avoid consuming toxic quantities of caffeine through moderation, with little effort.<sup>127</sup>

### III. Caffeine and the FDA: The Regulatory Framework

The United States maintains one of the world's safest supplies of food and drugs, thanks in large measure to the "interlocking monitoring system that watches over food production and distribution."<sup>128</sup> The Food and Drug Administration (FDA) is one of the focal points of this monitoring system, and has broad responsibilities regarding the oversight of foods, drugs, and other medical products.<sup>129</sup> The main regulatory authority for the FDA's work "originated with the Federal Food, Drug, and Cosmetic Act of 1938" (FDCA), though the powers and responsibilities of the FDA have been updated through legislation several times since its passage.<sup>130</sup> The FDA "regulates over \$1 trillion worth of products, which account for 25 cents of every

boosting ingredients," the total caffeine content of a pill this size is several ordinary doses, and likely accounts for the vast majority of the energy boost that a consumer will experience.

<sup>125</sup>For example, consumers may be unaware that guarana and similar "natural" ingredients contain caffeine naturally.

<sup>126</sup>See generally "Caffeine: The Problem of Disputed Science" section above.

<sup>127</sup>See Prothro, *supra* note 5 at 75: ("As with much else in our food and drug supply, moderation is the answer and should be the message conveyed by the FDA").

<sup>128</sup>See "Food Safety: A Team Approach," FDA Backgrounder, Sep. 24, 1998, available at <http://www.fda.gov/opacom/backgrounders/foodteam.html>.

<sup>129</sup>Sharon Wyatt Moore, "An Overview of Drug Development in the United States and Current Challenges," 96 SOUTHERN MED. J. 12, 1244 (Dec. 2003). See also "Food Safety," *supra* note 128, which outlines the overall U.S. government regulatory structure with regard to control over the food and drug supply, including the interlocking roles of the U.S. Department of Health and Human Services, the U.S. Department of Agriculture, the U.S. Environmental Protection Agency, and several other agencies.

<sup>130</sup>*Id.* at 1245.

dollar spent annually by American consumers.”<sup>131</sup>

#### A. Caffeine and the FDA: A Brief History of Dual Regulation

In general, FDA regulation requires that new drugs demonstrate that they are safe and efficacious for consumer use before companies market them to the public.<sup>132</sup> By statute, a drug is defined as any article “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.”<sup>133</sup> FDA regulation also ensures that the foods consumed by Americans on a daily basis are generally “safe and wholesome,” and that all of the food and drug products available to the public are “labeled truthfully with the information that people need to use them properly.”<sup>134</sup> Statute defines food as any article “used for food or drink”;<sup>135</sup> courts have further defined food in terms of “its function as food, rather than in terms of its source, biochemical

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<sup>131</sup>“The Food and Drug Administration: An Overview,” *available at* <http://www.cfsan.fda.gov/fdaoview.html>. *See also* “Health Information Resource Database,” National Health Information Center, *available at* [http://health.nih.gov/search\\_results.asp](http://health.nih.gov/search_results.asp); explaining the broad goals of the FDA: (“The mission of the U.S. Food and Drug Administration (FDA) is to: promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner; with respect to such products, protect the public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled; human and veterinary drugs are safe and effective; there is reasonable assurance of the safety and effectiveness of devices intended for human use; cosmetics are safe and properly labeled, and; public health and safety are protected from electronic product radiation; participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and, as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) of The FDA Modernization Act of 1997 (PL 105-115) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors and retailers of regulated products”).

<sup>132</sup>*See* Moore, *supra* note 129. A brief description of the evolution and scope of FDA authority follows: (“Although earlier drug legislation existed, this Act established the authority of the FDA to require that new drugs demonstrate safety before they could be marketed. The Kefauver-Harris Drug Amendments, passed in 1962, then required new drugs to demonstrate efficacy before marketing. In the 1970s, the FDA’s scope enlarged when the Public Health Service Bureau of Radiologic Health transferred to the FDA in 1971, the regulation of biologics transferred to the FDA from the National Institutes of Health (NIH) in 1972, and Medical Device Amendments were passed in 1976, establishing new regulatory procedures for medical device manufacturers. The Food and Drug Administration Act of 1988 officially established the FDA as an agency within the Department of Health and Human Services and noted that the President appoints the Commissioner of the FDA. This was followed by the Food and Drug Administration Modernization Act of 1997 (FDAMA), providing the most wide-ranging reforms in the FDA since 1938. The purposes of the FDAMA legislation included accelerated review of drugs and medical devices and regulation of advertising of unapproved uses of approved medical products”). *See also* <http://www.fda.gov>, for more general information regarding the FDA’s regulatory purview and history.

<sup>133</sup>21 U.S.C. 321(g)(1) (1994). The statute further includes any article (“other than food intended to affect the structure or any function of the body”).

<sup>134</sup>*See* “The Food and Drug Administration: An Overview,” *supra* note 131.

<sup>135</sup>21 U.S.C. 321(f) (1994).

composition or ingestibility.”<sup>136</sup>

Due to its content in such a wide variety of products, caffeine poses interesting regulatory challenges for the FDA, which “regulates caffeine extensively as a drug and a food.”<sup>137</sup> This kind of dual regulation is not at all uncommon; due to fact that the FDCA “has not been interpreted to require the definitions of food and drug to be mutually exclusive,”<sup>138</sup> the FDA instead tends to regulate substances that appear both in foods and drugs based on the advertising of the products.<sup>139</sup>

At first glance, it may seem odd that the same substance can be regulated ‘inconsistently,’ sometimes as a drug and other times as a food. For example, it may seem odd that chewing gum can be a drug simply because it contains caffeine and is advertised as a ‘natural energy booster.’ But this oddity is not limited to caffeine. . . .<sup>140</sup>

Moreover, definitions of articles adopted by the FDA are granted “substantial deference by courts.”<sup>141</sup>

Several factors generally apply to the FDA’s classification of a caffeine-containing product as either a food or a drug, the most important of which are: (1) whether the product is intended to be used for the diagnosis or treatment of disease; (2) whether it is intended to affect the body’s structure or its function; and most importantly - (3) the specific intent of the vendor.<sup>142</sup> Vendor intent “may be derived or inferred” based on the product’s “labeling, promotional material, advertising, and any other relevant source.”<sup>143</sup> Another

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<sup>136</sup> See Prothro, *supra* note 5 at 76, *citing* Nutrilab, Inc. v. Schweiker, 713 F.2d 335, 337 (7<sup>th</sup> Cir. 1983).

<sup>137</sup> See *Id.* at 75.

<sup>138</sup> See *Id.*

<sup>139</sup> See S. Rep. No. 74-361, at 4 (1935): (“If it is sold to be used both as a food and for the prevention or treatment of disease it would satisfy both definitions and be subject to the substantive requirements for both”). *Cited in* Prothro, *supra* note 5 at 75.

<sup>141</sup> See American Health Prods. Co. v. Hayes, 574 F. Supp. 1498, 1501 (S.D.N.Y. 1983), *aff’d per curiam*, 744 F.2d 912 (2d Cir. 1984). See also United States v. Neptone, holding (“the determination that Neptone is a drug rests entirely on the pattern of promotion used by claimant in the several years immediately preceding the instant seizure”).

<sup>142</sup> See National Nutritional Foods Ass’n v. Mathews, 557 F.2d 325, 333 (2d Cir. 1977): (“[t]he vendor’s intent in selling the product to the public is the key element in this statutory definition”).

<sup>143</sup> *Id.* at 334. See also Prothro, *supra* note 5 at 76-77: (“Thus, if one markets a caffeinated soft drink as just a soft drink, it will likely be regulated as a food. But if one markets it as a soft drink to help maintain ‘blood energy, muscular activity, sound teeth and gums,’ it will likely be regulated as a drug and require FDA pre-market approval”), *ref.* United States v. Kordel, 164 F.2d 913, 916 (7<sup>th</sup> Cir. 1947), *aff’d*, 335 U.S. 345 (1948); in which the “Kola” product sarsaparilla was declared a mislabeled

common factor in the FDA's calculus is whether or not the product is recognized in "official compendia";<sup>144</sup> however, while the courts generally grant extraordinary deference to the FDA's classification decisions, the courts are not in universal agreement about the application of this last factor.<sup>145</sup>

## B. Caffeine and the FDA I: Regulation as a Food

The FDA's choice in regulating caffeine either as a food or as a drug has important ramifications for the leniency or severity of the regulation imposed.<sup>146</sup> In general, the FDA's caffeine regulation is much less severe when applied to foods rather than drugs, though the level of leniency varies depending on whether caffeine is added to foods or occurs naturally.<sup>147</sup> Manufacturers of foods, dietary supplements, soft drinks, and many other ingestible consumer products generally prefer classification of their products as foods rather than as drugs, in order to benefit from the leniency of food regulation.<sup>148</sup> A spokesman for the FDA noted that

different regulations apply to drugs and foods. These differences include the labeling of the product, requirements for premarketing approval, practices required during manufacturing, the records that must be maintained during production and manufacturing, and the way in which the substance is dispensed.<sup>149</sup>

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drug as opposed to a food because it made health claims like a drug.

<sup>144</sup>See Prothro, *supra* note 5 at 76.

<sup>145</sup>See *e.g.* Mathews, *supra* note 142 at 337: ("the mere inclusion in the USP (United States Pharmacopeia) and the NF (National Formulary) is an insufficient basis for drug classification"). *But see* United States v. Beuthanasia-D Regular, [1979 Transfer Binder] Food Drug Cosm. L. Rep. P38265 (D. Neb. 1979); holding that such inclusion is conclusive evidence of drug status. *Cited in* Prothro, *supra* note 5 at note 80.

<sup>146</sup>See generally <http://www.fda.gov>, for a more complete description of the differences between food regulation and drug regulation.

<sup>147</sup>See Prothro, *supra* note 5 at 80. See also Prothro, *supra* note 5 at note 106: ("In coffee, tea and chocolate, for instance, caffeine occurs naturally and is nonadded. In soft drinks, however, caffeine is a food additive; only 5% of the caffeine present is naturally occurring <from the Kola nut>").

<sup>148</sup>See John Vanderveen, "Regulation of Amino Acids and Other Dietary Components Associated with Enhanced Physical Performance," Report from the Director of the FDA's Office of Plant and Dairy Foods and Beverages, Nov. 1992, *available at* <http://www.books.nap.edu/books/030905088X/html/461.html>.

With respect to each of the factors above, compliance with food regulation is both easier and less costly than compliance with corresponding drug regulation.<sup>150</sup>

Much of the FDA's past discussion of caffeine-containing foods revolved around the GRAS, or "generally regarded as safe," status of caffeine. Under statute, the FDA recognizes a wide variety of substances that satisfy GRAS; these substances include salt, pepper, vinegar, monosodium glutamate, common essential oils, spices, natural extracts, and artificial colors and flavors.<sup>151</sup> Caffeine as added to cola products has been a component of the GRAS list since 1961;<sup>152</sup> its use continues to be generally regarded as safe subject to a drug tolerance requirement of 0.02 percent by weight, and provided that it is added to sodas "in accordance with good manufacturing practice."<sup>153</sup>

The adherence to "good manufacturing practice" means that: (1) "the quantity of a substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritional, or other technical effect in food"; (2) "the quantity... that becomes a component of food" through processing or manufacturing "and which is not intended to accomplish any physical or other technical effect in the food itself, shall be reduced to the extent reasonably possible"; and (3) "the substance is of appropriate food grade and is prepared and handled as a food ingredient."<sup>154</sup>

By the FDA's estimation, soda manufacturers have thus far complied with these manufacturing requirements; therefore, caffeine is exempt from the provisions of the 1958 Food Additives Amendment and its successor

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<sup>150</sup>See generally Moore, *supra* note 129, for a more comprehensive analysis of the costs associated with drug regulation compliance.

<sup>151</sup>See 21 C.F.R. 182, at 456 (2003), available at <http://www.cfsan.fda.gov/~lrd/FCF182.html>.

<sup>152</sup>See 26 FED. REG. 938 (1961).

<sup>153</sup>See 21 C.F.R. 182, at 462 – "Subpart B—Multiple Purpose GRAS Food Substances, Sec. 182.1180," available at <http://www.cfsan.fda.gov/~lrd/FCF182.html>.

<sup>154</sup>21 C.F.R. 182, *supra* note 151 at 456. This regulation does bear the caveat that ("the inclusion of substances in the list of nutrients does not constitute a finding on the part of the Department that the substance is useful as a supplement to the diet for humans").

provisions through retention of GRAS status.<sup>155</sup> In the 1980s, however, GRAS status was somewhat in doubt:

In 1980, the FDA proposed to delete caffeine from the GRAS list, to declare that no prior “sanction” existed, and to restrict the use of caffeine in food to its 1980 levels until further studies could be conducted. It was prompted to issue the proposal by animal test results that suggested a link between caffeine and birth defects and raised concerns about caffeine’s potential teratogenicity.<sup>156</sup>

In 1987, following a finding that a 0.02 percent by weight requirement would be sufficient to protect the public from injury,<sup>157</sup> the FDA took strides in the opposite direction and instead proposed to grant a “prior exception” for caffeine as a soft drink additive.<sup>158</sup> To date, however, the 1987 proposal has not been acted upon, and caffeine remains on the GRAS list.<sup>159</sup>

Aside from GRAS status, the most obvious aspect of caffeinated food regulation is the requirement that caffeine appear in the list of ingredients when it is used as a food additive.<sup>160</sup> Interestingly, this regulation tends to apply primarily to soft drinks, and is not required in products that have natural caffeine content but no added caffeine. Moreover, the FDA does not require specific disclosure of the quantity of caffeine in food products, though some sources supply such information voluntarily.<sup>161</sup> While natural sources of caffeine, including coffees, teas, and chocolates go largely unregulated and unnoticed by the FDA,<sup>162</sup> the same cannot

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<sup>155</sup>See 21 U.S.C. 348 (1972), for a more complete listing of the requirements of the Food Additives Amendments.

<sup>157</sup>See 52 FED. REG. 18,923, 18,925 (1987).

<sup>158</sup>See 52 FED. REG. 18,923 (1987).

<sup>159</sup>See 21 C.F.R. 182, *supra* note 153 at 462. See also Prothro, *supra* note 5 at 81.

<sup>160</sup>See “How Are Additives Approved for Use in Foods?” Food Additives FDA/IFIC Brochure (Jan. 1992), *available at* <http://www.cfsan.fda.gov/~lrd/foodaddi.html>.

<sup>161</sup>For example, the list of ingredients on virtually any caffeinated soda product contains caffeine as a single ingredient in the list, along with all the artificial flavors, colors, and other additives used to preserve the product. However, information about the specific quantity of caffeine in popular products is readily available on the internet. See e.g. “Caffeine Content of Soft Drinks,” National Soft Drink Association (Oct. 2003), *available at* <http://nsda.org/WhatsIn/caffeinecontent.html>. See also “Caffeine Content of Foods and Drugs,” CSPI Press Releases (July 1997), *available at* <http://www.cspinet.org/new/cafchart.htm>, for a more comprehensive listing of caffeine content in common products.

<sup>162</sup>See Prothro, *supra* note 5 at 82.

be said for caffeine-containing substances regulated as drugs.

### C. Caffeine and the FDA II: Regulation as a Drug

Whether used as one of the world's first all natural energy drinks for shepherds and nomads, a religious zealot's device for maintaining all-night prayer, a sixteenth-century European panacea, or a modern miracle "wake-up" drug, caffeine has been used throughout the centuries for its stimulant effect.<sup>163</sup> In the United States today, however, pharmaceutical companies, food and beverage makers, and particularly over-the-counter producers of "energy products" are all subject to a wide variety of regulation, and cannot therefore market caffeine with reckless abandon.<sup>164</sup>

The FDA strictly controls the drug market and requires extensive showings of safety and effectiveness before it will allow caffeine (or any other drug) to be used as a drug ingredient. It does so 'to protect consumers and enable them to know what they're buying.'<sup>165</sup>

In order to regulate the behavior of American drug companies, the FDA publishes numerous documents involving product requirements and instructions; the two main types of documents are Regulations and Guidances.<sup>166</sup> The two document types differ in important ways: "Regulations are legally binding requirements found in Title 21 of the Code of Federal Regulations and must be followed," whereas Guidances "represent the FDA's current thinking and recommendations" but are nonbinding and subordinate to Regulations.<sup>167</sup> In order for any drug to be introduced into the market, it must conform to all codified FDA

<sup>163</sup> See "History of Caffeine," available at <http://web1.caryacademy.org/chemistry/rushin/StudentProjects/CompoundWebSites/1998/Caffeine/hi>. See also Goodman & Gilman, *supra* note 4 at 672.

<sup>164</sup> See Prothro, *supra* note 5 at 77.

<sup>166</sup> See Moore, *supra* note 129 at 1245.

<sup>167</sup> *Id.* Guidances also ("usually contain greater detail about specified topics and can be updated more easily").

regulations regarding safety and effectiveness.<sup>168</sup>

Once a company has submitted a drug for approval, the FDA will then review the company's application and issue a monograph classifying the drug.<sup>169</sup> A drug must receive a Category I monograph from the FDA before it can be marketed to the public; this means the FDA views the new product as safe, effective, and not misbranded.<sup>170</sup> A Category II classification means that the FDA must withhold market approval; by contrast, a Category III classification requires the petitioning company to obtain more data and submit for further FDA scrutiny prior to a final classification as either a Category I or Category II drug.<sup>171</sup>

Since technical information is essential to the process of drug approval, the FDA relies heavily on the independent expertise of advisory panels and committees.<sup>172</sup> The general role of an advisory panel is "to provide independent advice that will contribute to the quality of the agency's regulatory decision-making and lend credibility to the product review process."<sup>173</sup> This helps the FDA make better-informed decisions, while giving outside field experts the opportunity "to comment on whether adequate data supports approval, clearance, or licensing of a medical product for marketing," or suggest that additional information or labeling of a new product is necessary.<sup>174</sup> However, the most important fact about advisory panels is that their

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<sup>168</sup> See Prothro, *supra* note 5 at note 86: ("Every drug must be approved as safe and effective by the FDA before it can be introduced into interstate commerce"); See 21 U.S.C. 355(a) (1994). The Federal Food Drug and Cosmetic Act of 1938 initially imposed the drug "safety" requirement; this regulation was later updated to include drug effectiveness prior to introduction into interstate commerce. See 21 U.S.C. 355(b)(1)(a) (1994).

<sup>169</sup> Any company seeking new drug approval must submit applications to the FDA. An advisory review panel or committee generally reviews the application after several phases of testing. The FDA reviews the findings and final vote(s) of the advisory panel and then issues a monograph in response to the new drug application; this monograph will classify a new drug in one of three possible categories:

(1) Category I is applied if the new drug is "generally recognized as safe and effective and not misbranded"; (2) Category II is applied if the drug is not "generally recognized as safe and effective or would result in misbranding"; or (3) Category III is applied if the FDA determines that more testing data is required "on the basis of the Commissioner's determination that the available data are insufficient to classify such conditions" under either Category I or Category II. See 21 C.F.R. 330.10(a)(6)(i)-(iii) (1995). See also Prothro, *supra* note 5 at note 86.

<sup>170</sup> Prothro, *supra* note 5 at note 86.

<sup>171</sup> See *Id.*

<sup>172</sup> See Carol Rados, "Advisory Committees: Critical to the FDA's Product Review Process," FDA Consumer (Jan.-Feb. 2004), available at [http://fda.gov/fdac/features/2004/104\\_adv.html](http://fda.gov/fdac/features/2004/104_adv.html).

<sup>173</sup> *Id.*

<sup>174</sup> *Id.*

findings are nonbinding; “while committee decisions and final votes are very important to the FDA, the final regulatory decision rests with the agency.”<sup>175</sup>

In practice, the FDA has no problem disregarding the positive findings of an advisory panel. When caffeine was proposed as an addition to antacids in hangover medications in 1991, an advisory panel was convened regarding this proposal.<sup>176</sup> Following the advisory panel’s decision that the inclusion of caffeine would be safe and effective, the FDA disregarded the panel’s findings.<sup>177</sup> The agency concluded that

although moderate doses of caffeine did not generally cause gastrointestinal problems, the population likely to ingest hangover medicine already suffered from gastrointestinal irritation and might be harmed by caffeine’s stimulation of gastric secretions of hydrochloric acid.<sup>178</sup>

The agency therefore demonstrates that it adheres to a strict consumer safety policy regarding drug approval: the FDA can classify potentially useful drugs as unsafe solely on the basis that consumer usage of those drugs may ultimately be unsafe.<sup>179</sup>

The FDA has also demonstrated that failing any one of the three main approval criteria (safety, effectiveness, and proper labeling for stated purpose), is a sufficient rationale for the agency to withhold marketing approval. One clear example of this strict enforcement involves cold and allergy medications:

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<sup>175</sup>*Id.* See also “Human Drug Advisory Committees,” U.S. Food and Drug Administration Center for Drug Evaluation and Research, available at <http://www.fda.gov/cder/audiences/acspage/>, for more information regarding the appointment and function of advisory committees.

<sup>176</sup>See 56 FED. REG. 66,742 (1991).

<sup>177</sup>See 56 FED. REG. 66,746 (1991).

<sup>179</sup>See also “How Are Additives Approved for Use in Foods?” *supra* note 160, emphasizing the importance of FDA discretion with regard to “expected levels of human consumption.” The FDA often decides to prohibit or limit use of a product based on the idea that “the amount likely to be consumed” and “various safety factors” contribute to a belief that a potentially safe product will tend to be used unsafely.

For example, the FDA has prevented the use of caffeine in cold, cough, allergy, bronchodilator and antiasthmatic drug products because it concluded that caffeine was either unsafe or ineffective in combination with phenylpropanolamine and/or ephedrine or pseudoephedrine or in combination with any cold, cough, allergy, bronchodilator, or antiasthmatic ingredient, and either unsafe or ineffective (in combating lethargy) in cold preparations not containing antihistamines.<sup>180</sup>

It is interesting to note that the FDA does approve the use of theophylline, the methylxanthine closely related to caffeine, in bronchodilators because of its relaxing effects on smooth muscle; however, the quantity of caffeine required to make it an effective bronchodilator is considered close enough to its toxic quantity for the FDA to consider its use unsafe or ineffective.<sup>181</sup>

In reviewing caffeinated weight loss products like “Dexatrim,” the FDA, after advisory panel review, decided that both caffeine and caffeine citrate had no valuable weight loss effects for consumers; this prompted FDA intervention in 1991.<sup>182</sup> The agency both removed caffeinated weight loss products from the market and threatened further regulatory action against manufacturers if they refused to remove caffeine from their weight loss products within one year.<sup>183</sup> Even though caffeine intake has in the past been attributed to increased athletic function and metabolism, the FDA prefers to err on the side of caution and does not allow the public to overmedicate unnecessarily.<sup>184</sup>

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<sup>181</sup>See Goodman and Gilman, *supra* note 4 at 677. See also “What Are the Major Classes of Asthma Medications?” FAQ: Asthma – General Information (Sep. 2000), available at <http://www.radix.net/~mwg/medclass.html>, for a more detailed description of the FDA’s specific approval of different classes of asthma medications.

<sup>182</sup>See 21 C.F.R. 310.545(a)(20) (1995).

<sup>183</sup>See *Id.* See also 21 C.F.R. 310.545(d)(2) (1995).

<sup>184</sup>The FDA’s decision that caffeine does not correlate sufficiently with weight loss is under new scientific investigation. See e.g. M. H. Van Soeren and T.E. Graham, “Effect of Caffeine On Metabolism, Exercise Endurance, and Catecholamine Responses After Withdrawal,” available at <http://www.elitetrack.com/caffeine5.pdf>: (“We conclude the mechanism through which caffeine acts as an ergogenic aid is unlikely to be through changes in available metabolic substrates or catecholamines but rather is through some direct action of caffeine on tissues as yet to be described”). Whether caffeine stimulates increased metabolic function or acts in some other way to boost body energy, potential weight loss links could be reevaluated in the future following additional testing.

Setting aside the numerous instances in which the FDA has intervened in the consumer drug market to prevent unnecessary or unsafe caffeine use, a number of caffeinated drug products have been FDA-approved and are readily used by consumers.

FDA has approved the use of caffeine in a number of over-the-counter (OTC) drug products. For example, it has found caffeine to be safe and effective as an ingredient in stimulant drug products, used to ‘restore mental alertness or wakefulness during fatigue or drowsiness’... In addition, the FDA has approved the use of caffeine in menstrual drug products, recognizing that it is a diuretic and a stimulant which can help women suffering from water weight gain and fatigue during their menstrual or pre-menstrual periods. Finally, after years of study and review, the FDA has recognized the effectiveness of caffeine as an analgesic adjuvant in aspirin and aspirin/acetaminophen products.<sup>185</sup>

Caffeinate is often “widely employed” in the treatment of many ordinary types of headache and fatigue, and is even used in combination with an “ergot alkaloid in the treatment of migraine.”<sup>186</sup>

Once the FDA has approved the existence and production of a new caffeinated drug, it continues to monitor consumer safety through strict labeling requirements.<sup>187</sup> Contrary to caffeine food labeling requirements, which only require the presence of caffeine on the ingredients list if it is an additive (i.e. sodas), caffeine in drugs must be listed qualitatively on the label, and with significant stimulant warnings.<sup>188</sup> The regulation specifies that

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<sup>186</sup>See Goodman & Gilman, *supra* note 4 at 678.

<sup>187</sup>See generally <http://www.fda.gov>, for basic drug labeling requirements. See also Prothro, *supra* note 5 at 79.

<sup>188</sup>See 21 C.F.R. 340.50 (1995). Subsection (a) specifies that: (“the labeling of the product contains the established name of the drug, if any, and identifies the product as an ‘alertness aid’ or a ‘stimulant’”). Subsection (b) specifies the requirements for caffeinated product indications, but with the important restriction that: (“Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed...”); meaning that the FDA still pull the product from the market even if the label is technically correct if they find that consumers are being misled.

The labeling of the product contains the following warnings under the heading ‘warnings’:

- (1) The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.
- (2) For occasional use only. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a physician [or doctor].
- (3) Do not give to children under 12 years of age.<sup>189</sup>

Furthermore, in 1999, the FDA approved a new monograph (generally effective in April 2001) with more detailed labeling requirements for over-the-counter drugs.<sup>190</sup>

Among the new over-the-counter labeling provisions are requirements that the labels “adhere to standardized headings and subheadings, presented in a specified order,” as well as graphical restrictions including “minimum requirements for type size, graphical highlights, leading (space between two lines of text), kerning (spacing between letters),” and use of “connecting terms” previously required under the Code of Federal Regulations.<sup>191</sup> The updated regulation is intended to “further the safe and effective use of these drug products for consumers by making labels easier to read and understand.”<sup>192</sup>

The FDA’s continuing concerns regarding the labeling and warnings on caffeinated drugs are part of the agency’s dedication to further minimizing consumer health risks. For example, one of the reasons the FDA mandates standardized and legible drug content data is so that consumers can avoid using too much caf-

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<sup>190</sup> See generally “New FDA Labeling Requirements for Over-the-Counter Drug Products,” Release #9B-118 (Sept. 1999), available at <http://www.actstesting.com/actsnews.nsf/0/860825D224E2E73285256802004637F3?open>.

<sup>191</sup> See *Id.* Companies like ACTS Testing Labs (the sponsor of the site) are paid by companies to evaluate new drug labels for potential FDA compliance problems.

<sup>192</sup> *Id.* Another separate issue of ever-increasing importance is the labeling of prescription drugs. In the December 22, 2000 Federal Register, a new FDA prescription drug labeling proposal was put forth, in response to (“increasing length and complexity of labeling for new prescription drugs, and after many physicians said the current format can lead to confusion. The agency states that the information most useful to doctors is contraindications, drug interactions, side effects, and dosage and administration”). See “FDA Caters to Physicians; A Proposed Rule for Redesigning Prescription Drug Labeling Can Help Save Physician Time and Reduce Adverse Drug Events,” (Mar. 2001), available at <http://devicelink.com/pmpn/archive/01/03/010.html>. This further underscores the importance the FDA places on accurate and safe labeling of drugs, and the difficulties in protecting the consumer public; if expert physicians are having difficulty understanding and safely dispensing prescription medication, the FDA is even more concerned about the ramifications of consumer self-medication with readily available over-the-counter drugs.

feine in combination with other products, therefore both making consumers aware of likely side effects and reducing the potential for negative consequences from these side effects.<sup>193</sup>

Perhaps the most important addition to the existing over-the-counter drug regulations is the codification of active ingredient listing requirements including the specific quantity of ingredients used. Prior to the 1999 final rule on over-the-counter labeling requirements, the FDA did not require manufacturers to list the quantities of active ingredients on their labels.<sup>194</sup> Some sources posit that such regulation was, in the past, unnecessary due to massive voluntary disclosure of active ingredient information; “under another voluntary program begun in 1974, the member companies . . . have been including the quantities of active ingredients on OTC drug labels.”<sup>195</sup> The Nonprescription Drug Manufacturers Association, a trade organization that encompasses the vast majority of all over-the-counter drug sales in the United States, was the impetus for this general practice of voluntary disclosure.<sup>196</sup>

As part of the 1999 reforms, and partly due to the tremendous increase in the publicly available number of herbal remedies, energy boosting supplements, and other new over-the-counter drug products, the FDA issued regulations that codified the previous voluntary practice of active ingredient quantity labeling.<sup>197</sup>

Under the “Active Ingredients” section of the final rule, the FDA notes that

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<sup>193</sup>See Prothro, *supra* note 5 at 79-80. See also 53 FED. REG. at 6,100 and 6,103, discussing stimulant warning statements.

<sup>194</sup>See “Over-the-Counter Human Drugs: Labeling Requirements,” FDA Final Rule Re: 21 C.F.R. Parts 201, 330, 331, 341, 346, 355, 358, 369, and 701 (Mar. 1999), available at <http://www.fda.gov/cder/otc/label/label-fr-reg.htm>.

<sup>195</sup>See 60 FED. REG. 6,892, 6,897 (1995), cited in Prothro, *supra* note 5 at note 105. See also “Over-the-Counter Human Drugs: Labeling Requirements,” *supra* note 194: (“At that time, the agency’s regulations encouraged (but did not require) manufacturers to include the quantity per dosage unit in the labeling (330.1(j)). The vast majority of OTC drug products already include such information in their labeling”).

<sup>196</sup>See *Id.*

<sup>197</sup>See “Over-the-Counter Human Drugs: Labeling Requirements,” *supra* note 194: (“As a result of the statutory change, this final rule makes clear that the established name and quantity of each active ingredient must be included in the required information set forth in 201.66(c), in the location and format established by the agency”).

Section 201.66(c)(2) requires the heading “Active Ingredient(s),” followed by the established name and the quantity of each active ingredient per dosage unit. For products marketed without a discrete dosage unit, such as topical OTC drug products, the proportion of each active ingredient must be stated instead of the quantity, unless otherwise specified in an applicable monograph or approved drug application. This provision incorporates a recent amendment to section 502(e) of the act under FDAMA. . . to require that the quantity. . . of each active ingredient appear in the labeling of all OTC drug products intended for human use.<sup>198</sup>

This means that consumers can now be certain to know exactly how much caffeine they consume when using over-the-counter drugs. While there is still “a significant discrepancy in caffeine content across OTC drugs,” consumers are “made aware of it and are warned against excessive consumption.”<sup>199</sup>

Another way the FDA maintains control over caffeinated drugs after market approval is through dosage limits; for example, while certain analgesics use caffeine both as an adjuvant and a stimulant, the FDA planned to limit the amount of caffeine to “64 or 65 mg per dose irrespective of the amount of analgesic in the dose.”<sup>200</sup> The low dosage was the “demonstrated minimum effective caffeine dose, and was chosen based on agency concerns about the potential of caffeine to foster analgesic misuse.”<sup>201</sup> Because the FDA perceives caffeine habituation as a problem, albeit a reasonably minor one, drugs that incorporate caffeine must still do so at doses that are clinically effective while not unnecessarily or deliberately causing addictive psychotropic responses.<sup>202</sup>

Even in drug products in which the FDA generally allows caffeine to be used in small amounts, such as

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<sup>199</sup> See Prothro, *supra* note 5 at 80.

<sup>200</sup> See F.D.C. REP., 3 THE TAN SHEET 19 (1995), *cited in* Prothro, *supra* note 5 at note 99.

<sup>201</sup> See *Id.*, *cited in* Prothro, *supra* note 5 at 79.

<sup>202</sup> See *Id.*: (“Habituation to caffeine is well documented in the scientific literature. . . caffeine in analgesic combinations at concentrations as low as 64 mg can exert some psychotropic effect”).

aspirin or acetaminophen pain relievers, approval does not extend unequivocally to any similar class of drug seeking to include caffeine. Further, even if permission is granted to produce and market a new drug, there is still strict FDA supervision of marketing claims made on behalf of caffeine-containing drugs.<sup>203</sup> For example, in 1997, Bristol-Myers Squibb attempted market a new caffeine-containing drug similar to a commonly used pain reliever called “Norflex,” which contains the active ingredient orphenadrine citrate.<sup>204</sup>

Norflex (orphenadrine citrate) is used “to relieve the pain and discomfort associated with musculoskeletal injuries and conditions.”<sup>205</sup> In its attempt to market its new tablet combining orphenadrine citrate, aspirin, and caffeine, Bristol-Myers Squibb and its subsidiaries released promotional materials claiming this new tablet was “AB Rated, Therefore Bioequivalent to Norflex.”<sup>206</sup> However, the FDA demanded immediate removal of all promotional material, stating that “Norflex contains only a single active agent, namely, orphenadrine citrate. . . . thus these products are not AB rated and are not bioequivalent.”<sup>207</sup> The FDA was primarily concerned about the potential for interaction effects that could result from the use of the additional active ingredients caffeine and aspirin combined with orphenadrine citrate.<sup>208</sup> Thus, even after approval, the FDA maintains a vigilant watch over the caffeine-containing consumer drug pool in order to minimize the potential for negative health consequences among consumers.

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<sup>203</sup> See generally Moore, *supra* note 129.

<sup>204</sup> See Stephen Sherman, “Warning Letter to Thomas E. Costa, Vice President and Counsel, U.S. Pharmaceutical Group, Bristol-Myers Squibb Company Re: ANDA 74-817 Orphenadrine Citrate, Aspirin and Caffeine Tablets,” FDA Division of Drug Marketing, Advertising and Communications (July 1997), available at <http://www.fda.gov/cder/warn/july97/orphen.pdf>.

<sup>205</sup> See “Orphenadrine Citrate Drug Information,” Pharmacy Health (2003), available at <http://www.pharmacyhealth.net/d/orphenadrine-citrate-6471.htm>.

<sup>206</sup> See Sherman, *supra* note 204.

<sup>207</sup> *Id.*

<sup>208</sup> See *Id.*: (“There is significant risk and potential danger to consumers if Apothecan’s product were used inadvertently in place of Norflex by a consumer who is allergic to aspirin or who has peptic ulcers or coagulation abnormalities. . . . BMS should immediately, clearly, and prominently alert health care professionals of this serious error, that its orphenadrine citrate, aspirin and caffeine tablets are not bioequivalent to Norflex, and the potential risks of using this product. . .”).

#### IV. The Future of Caffeine Regulation: Reexamining the FDA Approach

Recognizing the American public's curious infatuation with caffeine, the FDA, through its regulation of both foods and drugs, has been trying to keep the public informed about caffeine and protected from any adverse effects. In the 1980s, after data suggested a correlation between caffeine and birth defects, the FDA was hard at work, issuing press releases, consumer warnings, and labeling requirements as part of its educational campaign.<sup>209</sup> As with any food or drug, as the FDA perceives consumer health concerns, it intervenes to correct problems through issuance of regulations and through direct contact with manufacturers.<sup>210</sup> If no way can be found to release and market a particular product such that it will be safe and effective for consumer use, the FDA issues an order to pull the product from the market entirely.<sup>211</sup>

##### A. More FDA Regulation: No Additional Need, No Productive Purpose

To date, the FDA has not seen fit to issue a general ban on the inclusion of caffeine in foods and drugs because such a ban is unwarranted. Since caffeine has been used safely for so long in so many foods and beverages, a simple risk-benefit calculus would lead to the general conclusion that "consumers be permitted to make their own judgments about risks on the basis of complete and accurate information about the hazards involved."<sup>212</sup> With the dearth of long-term caffeine study data raising alarm, and the prevalence of caffeine in the consumer products market, the FDA should remain on guard for future indications of dangerous health correlations.

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<sup>209</sup> See Prothro, *supra* note 5 at 82-83 for further summary.

<sup>210</sup> See generally "About the U.S. Food and Drug Administration," available at <http://www.fda.gov/opacom/hpview.html>.

<sup>211</sup> See *Id.*

<sup>212</sup> Peter B. Hutt, "The Basis and Purpose of Government Regulation of Adulteration and Misbranding of Food," 33 FOOD DRUG COSM. L. J. 505, 537 (1978).

However, following the recent passage of uniform over-the-counter drug labeling requirements,<sup>213</sup> there is no further market intervention that would be necessary or desirable on the part of the FDA.

Some sources have suggested that there is a problem with caffeine regulation as applied to foods, asserting that caffeine content labeling on foods is the next logical step in FDA consumer protection.<sup>214</sup> The basic argument for this position is that consumers cannot make informed choices about their daily caffeine intake if the specific amount of caffeine is only listed on certain drug products.<sup>215</sup> The argument also notes that “caffeine quantities vary significantly in foods,” and generalizes that consumers may be misled if, for example, a single serving of chocolate can contain anywhere from six to twenty-five milligrams of caffeine.<sup>216</sup>

Any argument that favors the extension of caffeine quantity labeling to foods is fundamentally flawed. While it might be beneficial to know the exact amount of caffeine in any given food, this is not always possible. A new coffee study suggests (among other things) that “java’s caffeine jolt varies naturally,” and that “there are many variables that contribute to caffeine content from cup to cup, such as the type of bean, roasting and brewing methods, and grind.”<sup>217</sup> This variance is further exacerbated by recent findings that “the caffeine content of specialty coffee beverages varies widely from day to day as well as from coffee shop to coffee shop.”<sup>218</sup>

While the study data suggests that American caffeine consumption may be on the rise, researchers contend

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<sup>213</sup> See “Over-the-Counter Human Drugs: Labeling Requirements,” *supra* note 194.

<sup>214</sup> See Prothro, *supra* note 5 at 83.

<sup>215</sup> See *Id.*

<sup>216</sup> See *Id.*

<sup>217</sup> See Jennifer Warner, “Specialty Coffee’s Caffeine Jolt Varies,” WebMD Health Archives (Oct. 23, 2003), *available at* <http://my.webmd.com/content/article/75/89869.htm>, *ref.* R. McCusker, 27 J. ANALYTICAL TOXICOLOGY 520, 520-522 (Oct. 2003).

<sup>218</sup> *Id.* The study refers to a comparison between “Starbucks” coffee and “Dunkin Donuts” coffee, and finds that the average medium sized coffees from Starbucks contained 259 milligrams of caffeine, as compared to 143 milligrams of caffeine for Dunkin Donuts coffee. Further, the study noted that at identical storefront locations, the caffeine content of a Starbucks medium coffee could range anywhere from 259 to 564 milligrams.

that “coffee drinkers might have to live with uncertainty when it comes to how much caffeine” they take in from their daily coffee.<sup>219</sup> This same logic applies to all other natural sources of caffeine in foods; if the caffeine content in a serving of chocolate can vary anywhere from six to twenty-five milligrams, it would be an unjustifiable burden on manufacturers to have them give a best guess at the caffeine content on an individual item. Further, the quantity of caffeine added to products like soda, while not listed explicitly on the label, is easily enough obtained since content data is published by soft drink manufacturers.<sup>220</sup>

Fortunately, the FDA has long held to a policy of rarely including consumer health warnings on foods, and doing so only in such instances deemed absolutely necessary.<sup>221</sup> The fact that caffeine has been safely consumed for so long, coupled with the agency’s fear of consumer analysis paralysis, suggests that further regulatory intervention is both impractical and undesirable.<sup>222</sup>

#### B. New Scientific Information Means Diminished Concern

The advancement of new scientific data regarding the positive and neutral health impacts of caffeine prompted the FDA’s public affairs staff to summarize some of the administration’s previous concerns about caffeine.<sup>223</sup>

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<sup>219</sup> *See Id.*

<sup>220</sup> *See e.g.* “Caffeine in Beverages,” available at <http://www.nstda.org/WhatsIn/caffeinecontent.html>. The National Soft Drink Association voluntarily makes caffeine content data public.

<sup>221</sup> *See* 58 FED. REG. 2850, 2872 (1993).

<sup>222</sup> *See e.g.* Lars Noah, “The Imperative to Warn: Disentangling the ‘Right to Know’ from the ‘Need to Know’ About Consumer Product Hazards,” 11 YALE J. ON REG. 293, 315-20 (1994). *See also* Prothro, *supra* note 5 at 86, admitting: (“[a] caffeine warning label would not be useful. There are simply too many labels ‘warning’ consumers. Their combined effect is overload. Consumers react either by ignoring all warnings, including ones of deadly danger, or by paying too much attention to the warnings and avoiding all products bearing such statements, including useful and beneficial products”).

<sup>223</sup> *See* Chris Lecos, “Caffeine Jitters: Some Safety Questions Remain,” FDA Public Affairs Staff, available at <http://www.hoptechno.com/book4.htm>.

In 1980, FDA was confronted with various studies that aroused concern about the possible association of caffeine in the human diet with numerous health problems. Of immediate concern was the study that demonstrated caffeine's potential for causing birth defects in animals. Was there a danger to humans? The agency said that it didn't know. So, it chose to lean on the side of caution by warning pregnant women and, at the same time, asking industry and the scientific community to do more studies on caffeine's health effects. These have now been done, and they generally have produced less worrisome results. For that reason, and because FDA determined that some of the earlier studies were faulty, inconclusive, or contradicted by later findings, the concern about caffeine has lessened.<sup>224</sup>

A change in the regulatory posture of caffeine is unsurprising, as the FDA continues to monitor and update the level of regulation on consumer products based on the continued development of laboratory data.<sup>225</sup> What is surprising, however, is the continued outpouring of new data suggesting potential positive health effects of caffeine use. For example, the National Parkinson Foundation has researched the posited inverse relationship between caffeine intake and Parkinson disease for years, but with "equivocal" results at best.<sup>226</sup> However, a thirty-year follow-up case review published in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION indicates that "higher coffee and caffeine intake is associated with a significantly lower incidence of Parkinson disease."<sup>227</sup> While it is certainly not the last word on this newly-established caffeine correlation, it serves as proof-positive that time and medical data can and have significantly diminished the necessary level

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<sup>225</sup> See generally <http://www.fda.gov>, for information regarding continuing post-approval regulation of food additives and drugs.

<sup>226</sup> See Abraham Lieberman, "Coffee and Parkinson Disease: Is Starbucks the Treatment?" National Parkinson Foundation (2000), available at <http://www.parkinson.org/coffee.htm>.

<sup>227</sup> *Id.*; describing a May 2000 study released in the JAMA that involved 8,004 Japanese-American men over a period of 30 years. The study utilized ("Incident Parkinson disease (number of participants who developed Parkinson during the study) by amount of coffee intake (measured at study enrollment and 6-year follow-up) and by total dietary caffeine intake (measured at enrollment)...") as its main outcome measure, and further found that: ("Age-adjusted incidence of Parkinson disease declined consistently with increased amounts of coffee intake, from 10.4/10,000 person-years in men who drank no coffee to 1.9/10,000 person-years in men who drank at least 280z/d. Similar relationships were observed with total caffeine intake and caffeine from non-coffee sources... Other nutrients in coffee, including niacin, were unrelated to Parkinson disease incidence. The relationship between caffeine and PD was unaltered by intake of milk and sugar"). See also Tomas DePaulis, PhD research scientist for Vanderbilt University's Institute for Coffee Studies, quoted in Sid Kirchheimer, "Coffee: The New Health Food? Plenty of Health Benefits Are Brewing in America's Beloved Beverage," WebMD Feature (Jan. 26 2004), available at <http://content.health.msn.com/content/article/80/96454.htm?printing=true>: ("In fact, Parkinson's drugs are now being developed that contain a derivative of caffeine based on this evidence").

of public health concern with regard to caffeine use.

Another example of conflicting

caffeine data that has been reconsidered recently involves correlations between caffeine intake and health risks for women who are either seeking to become pregnant, or who are already pregnant or nursing. A small 1988 study suggested that low to moderate caffeine consumption might decrease female fertility; however, the scientists involved “acknowledged that delayed conception could be due to other factors they did not consider, such as exercise, stress, or other dietary habits.”<sup>228</sup> Further study data has since prompted the International Food Information Council (IFIC) to dismiss the presumed link between caffeine and infertility.<sup>229</sup> The IFIC and the Organization of Teratology Information Services (OTIS) further investigated correlations between caffeine intake and risks of birth defects, low birth weight, and caffeine transfer to infants through breast milk; the results demonstrate that, though high levels of caffeine intake are potentially dangerous to infants during gestation and breast feeding, low to moderate levels of caffeine intake are less problematic than previously thought.<sup>230</sup>

The wave of recent positive caffeine study data has even caused some health professionals and consumers to wonder if coffee is “the new health food.”<sup>231</sup> Besides posited correlations between caffeine intake and reduced risk of Parkinson disease, a recent Harvard study also suggests that persistent caffeine use might also reduce the risk of type-2 diabetes.<sup>232</sup>

<sup>228</sup> See “Caffeine, CERHR Study,” *supra* note 89.

<sup>229</sup> See *Id.*: (“Since then, larger, well-designed studies have failed to support these findings. In 1990, researchers at the Centers for Disease Control and Prevention and Harvard University examined the association between the length of time to conceive and consumption of caffeinated beverages. . . . The researchers found that caffeine consumption had little or no effect on the reported time to conceive in those women who had given birth. Caffeine consumption also was not a risk factor for infertility. [In] 2001, OTIS reviewed the studies examining caffeine effects on fertility and concluded that ‘low to moderate caffeine consumption (<300mg/day) does not seem to reduce a woman’s chance of becoming pregnant’”).

<sup>230</sup> See *Id.*: (“Groups such as OTIS, March of Dimes, and Motherisk reviewed studies examining caffeine intake during pregnancy and are in agreement that high caffeine intake (>300mg/day, equivalent to more than 3 cups of coffee/day) should be avoided during pregnancy. There is also general agreement that low caffeine intake (<150mg/day, about 1-1/2 cups of coffee) during pregnancy is not likely to harm the unborn child. See also “Caffeine and Women’s Health,” *supra* note 4. See also “Caffeine in Pregnancy,” March of Dimes Quick Reference and Fact Sheets (April 2004), available at [http://www.marchofdimes.com/professionals/681\\_1148.asp](http://www.marchofdimes.com/professionals/681_1148.asp). See generally “Caffeine and Pregnancy,” Organization of Teratology Information Services (Dec. 2001), available at <http://www.otispregnancy.org/pdf/caffeine.pdf>).

<sup>231</sup> See Kirchheimer, *supra* note 227.

<sup>232</sup> See *Id.*, *ref.* Harvard School of Public Health study by Frank Hu, 140 ANNALS OF INTERNAL MED. 1, 1-8 (Jan 2004).

After analyzing data on 126,000 people for as long as 18 years, Harvard researchers calculate that compared with not partaking in America's favorite morning drink, downing one to three cups of caffeinated coffee daily can reduce diabetes risk by single digits. But having six cups or more each day slashed men's risk by 54% and women's by 30% over java avoiders.<sup>233</sup>

While these (and other similar) findings would benefit from more research, the overarching trend in caffeine data over the last five to ten years is positive; "overall. . . coffee is far more healthful than it is harmful. . . the evidence is very strong that regular coffee consumption reduces risk of Parkinson's disease and for that, it's directly related to caffeine."<sup>234</sup>

The proliferation of scientific information available through the internet has a large upside for consumers: useful findings of new medical studies (including the ones discussed herein) can reach the consumer public faster than ever before. Internet services such as "MSN Health" and "WebMD" even have newsletter services, such that health product consumers can make more informed product purchasing decisions as a result of newly available information.<sup>235</sup> For caffeine users, this translates to increased awareness of product effects, such that people can better regulate their diets to suit their individual health needs.<sup>236</sup>

### C. Residual Skepticism and Incomplete Scientific Information

The availability of new caffeine health data does not mean that the FDA should rest on its regulatory laurels. The Parkinson disease, pregnancy, and diabetes studies together illustrate that with the increase in the number of scientific experiments conducted and the dramatic expansions of available scientific data and information, the FDA and the American public (as consumers of health information) must be cautious not to jump too quickly to health-related conclusions. The Parkinson study admits that "the study design is such as to prevent the researchers from concluding, definitively, that coffee or caffeine directly protect against development of

<sup>234</sup> See *Id.*, quoting Tomas DePaulis, PhD research scientist for Vanderbilt University's Institute for Coffee Studies.

<sup>235</sup> See *e.g.* <http://www.webmd.com>, and <http://www.health.msn.com>; website visitors can subscribe to particular categories of health-related newsletters, such that they will be emailed new updates on their topics of choice.

<sup>236</sup> See *Id.* Thousands of visitors frequent WebMD daily; an in-site search for "caffeine" yielded 722 documents discussing different aspects of caffeine, including latest medical findings. Arguably, this means that new information is readily available to consumers.

Parkinson disease.”<sup>237</sup> It instead recognizes that “the possibility that caffeine may have a protective effect against developing Parkinson disease must be investigated further.”<sup>238</sup> The FDA admits that the risks associated with caffeine use have been at least overstated in the past;<sup>239</sup> even so, sources at the FDA continue to encourage consumer wariness, fearing unknown future potential effects from long-term exposure.

However, FDA is also saying that while there is a basis for being less concerned about caffeine’s impact on health, some questions remain unanswered. The agency continues to stress that caffeine is a chemical stimulant that affects the central nervous system. It is a widely used food additive to which some people are more sensitive than others. It could have other, still unknown, effects. But determining what these effects are is not a simple matter, as some studies have indicated, since other factors - such as smoking, alcohol consumption, poor diet, and drug use - also can affect human health. From a regulatory standpoint, FDA will continue to monitor caffeine use in foods and how much of it people consume. Meanwhile, consumers probably should adhere to some age-old advice: moderation makes good sense.<sup>240</sup>

Many consumers also decry the lack of caffeine content data on food products such as sodas, fearing the addictive properties of the drug are more dangerous than the FDA recognizes.<sup>241</sup>

Besides the obvious potential problems with new scientific data, including consumer over-reliance and incomplete or uncertain conclusions, caffeine and other drug data can be taken out of context or manipulated in such a way as to cause an artificial sense of consumer security or unnecessary fear of drug products. For ex-

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<sup>237</sup> See Lieberman, *supra* note 226. The study also humorously notes that: (“At this time there is not enough evidence to urge you to go to Starbucks and drink 6 café-lattes a day”).

<sup>238</sup> *Id.*

<sup>239</sup> See “Caffeine Jitters,” *supra* note 223.

<sup>241</sup> See *e.g.* Patricia Lieberman, “Label Caffeine as a Drug – Even in Soda,” New York Times Letter to the Editor, Aug. 26, 1997, available at <http://www.junkscience.com/news/soda.html>: (“[t]he article ignored one of the worst aspects of adding caffeine to soda. Introducing a mildly addictive drug to soft drinks encourages children to drink sugar water instead of more nutritious beverages like fruit juice and low-fat milk. . . . The Food and Drug Administration should require that soft drinks and other foods be labeled with their caffeine content to help parents decide what their children should drink”).

ample, a recent alarmist email message was sent to thousands of consumers regarding phenylpropanolamine, a common product in cough and cold medicines, weight control drugs, and decongestants.<sup>242</sup> Among other claims, the email letter suggested that “all drugs containing phenylpropanolamine are being recalled,” and that consumers should “stop taking anything containing this ingredient” because it “has been linked to increased hemorrhagic stroke. . . among women ages 18-49 in the three days after starting use of medication.”<sup>243</sup> While it is true that the FDA is seriously concerned over the inclusion of phenylpropanolamine in common over-the-counter products, particularly after a Yale research study linked it to increased risk of hemorrhagic stroke,<sup>244</sup> the FDA already took the necessary regulatory measures in the year 2000.<sup>245</sup> Further, the email letter grossly overstates the linkage between phenylpropanolamine and immediate health risk.<sup>246</sup>

The “drug hoax” as described is not included to suggest that FDA and other consumer health warnings should be taken lightly; rather, it serves to illustrate the downside of the information age. With the explosion of internet technology, consumers live in an age in which scientific information is more readily available than ever before, and this has consumer awareness benefits.<sup>247</sup> With this new ease of access to data comes a corresponding responsibility to carefully consider the sources and validity of available information, the overarching concern being that the quality of health related statements relied upon by consumers is oftentimes dubious. Provided that consumers stick to reputable sources of information, however, increased connectivity

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<sup>242</sup> See “Drug Recall Hoax,” Trend Micro Security Info (2004), available at <http://www.trendmicro.com/vinfo/hoaxes/hoax5.asp?HName=Drug+R>  
<sup>243</sup> *Id.*

<sup>244</sup> See Ralph Horwitz et al., “Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of The Hemorrhagic Stroke Project,” (May 10, 2000), available at <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3647b1.tab19.doc>.

<sup>245</sup> See “Phenylpropanolamine (PPA) Information Page,” CDER (2000), available at <http://www.fda.gov/cder/drug/infopage/ppa/default.htm>: (“The Food and Drug Administration (FDA) is taking steps to remove phenylpropanolamine (PPA) from all drug products and has requested that all drug companies discontinue marketing products containing PPA. In addition, FDA has issued a public health advisory. . .”).

<sup>246</sup> While the letter described the health risks as “URGENT,” the FDA concluded that: (“Although the risk of hemorrhagic stroke is very low, FDA recommends that consumers not use any products that contain PPA”). See “Phenylpropanolamine (PPA) Information Page,” *supra* note 245. See also “Drug Recall Hoax,” *supra* note 242.

<sup>247</sup> See generally “New Scientific Information Means Diminished Concern” section above.

can lead to better health decision-making.<sup>248</sup>

#### D. A Hypothetical Scenario Considered: Caffeine as a New Food Additive or Drug

Though the policy of consumer moderation is still an entirely sensible approach, this Paper generally contends that, in the face of newer and better data, caffeine is much safer than older studies and reviews have suggested. This finding, however, prompts an interesting hypothetical consideration: since caffeine is and has been so pervasive in the marketplace (naturally, as a food additive, and in drugs), it has not been forced to undergo the more complex and time consuming contemporary processes of food additive or drug approval. It is worthwhile, then, to hold caffeine up to current regulatory process and scrutiny, in order to better demonstrate that previous health concerns regarding caffeine were inflated.

##### 1. Caffeine as a Newly-Proposed Food Additive

A company must first petition the FDA for approval before marketing a new food additive.<sup>249</sup> A food additive petition “must provide convincing evidence that the proposed additive performs as it is intended.”<sup>250</sup> Usually, part of the relevant data comes from animal studies “using large doses of the additive for long periods” to satisfactorily demonstrate that the substance “would not cause harmful effects at expected levels

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<sup>248</sup> See e.g. <http://www.webmd.com>, which is a highly trafficked and well respected contemporary source of consumer health information.

<sup>249</sup> See “How Are Additives Approved for Use in Foods?” *supra* note 160.

<sup>250</sup> *Id.*

of human consumption.”<sup>251</sup> The FDA considers many factors, including “the composition and properties of the substance, the amount likely to be consumed, its probable long-term effects and various safety factors” when weighing its approval decisions.<sup>252</sup> Since one-hundred percent safety is not practical for any substance, the FDA must instead determine if the proposed new additive is safe enough “under the proposed conditions of use,” and “based on the best scientific knowledge available.”<sup>253</sup>

Now, assume the existence of a new soda company, “Hypo-Cola,” in a consumer world that is entirely familiar with the GRAS list and with the proper process for soda manufacturing, but that is caffeine naïve. First, the Hypo-Cola company petitions the FDA to have its new additive, the methylxanthine chemical caffeine, approved for consumer use.<sup>254</sup> As a potential new food additive, the FDA wants to know caffeine’s intended purpose, as well as the company’s rationale for including it in its new soft drink.

This is the first potential snag in the regulatory process; without GRAS list status, and without a world in which caffeine use is assumed to be both natural and commonplace, Hypo-Cola likely has some difficulty explaining the need for caffeine’s inclusion in sodas. While the National Soft Drink Association claims both that “caffeine has a classic bitter taste that enhances other flavors,” and that “small amounts of caffeine are added to soft drinks as part of the flavor profile,”<sup>255</sup> Hypo-Cola has to convince the FDA of the validity of those claims while minimizing the significance of the chemical’s stimulant properties, or else risk more cumbersome drug regulation.

Getting caffeine approved as a flavor additive may be slightly more difficult in light of a recent Johns Hopkins

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<sup>251</sup>*Id.* The FDA also notes that: (“approximately 100 new food and color additives petitions are submitted to the FDA annually”), though most are for (“indirect additives such as packaging materials”). Further, any available human study data may be submitted to the FDA along with animal test data.

<sup>252</sup>*Id.* See generally “Food Safety: A Team Approach,” *supra* note 128.

<sup>253</sup>*Id.*

<sup>254</sup>For purposes of this hypothetical exercise, assume that all the current laboratory data on caffeine is known to the scientific and regulatory communities.

<sup>255</sup>See “What’s In Soft Drinks?” National Soft Drink Association (Oct. 2003), available at <http://www.nsd.org/softdrinks/History/whatsin.html>.

University study, which found that “only two out of 25 hard-core cola drinkers were able in a blind taste test to detect whether a soda sample contained caffeine.”<sup>256</sup> While the size and format of the study are disputed by the National Soft Drink Association,<sup>257</sup> the results might cause the FDA to take a closer look at caffeine’s inclusion in new soft drinks, and the potential for mandatory labeling requirements. However, since “vendor intent” is a strong indicator of whether a substance will be considered a food or a drug,<sup>258</sup> and since there is not sufficient evidence to suggest ulterior motivation on the part of soda manufacturers, Hypo-Cola can likely proceed with the FDA approval process.<sup>259</sup>

The FDA then considers the chemical properties of the new additive, potential consumer use of the product (including the amount likely to be consumed), and the likelihood of long-term consumer health risks. Hypo-Cola has to provide evidence sufficient to satisfy the FDA’s consumer safety concerns.<sup>260</sup> Assuming the company has mustered all relevant study data, including sufficient animal laboratory data to show that the stimulant effects of caffeine are generally harmless, and further assuming that Hypo-Cola will be using a small enough amount of caffeine so as not to injure public health,<sup>261</sup> the FDA might approve the use of caffeine as a new soft drink flavoring additive.

If a new additive is approved, the FDA “issues regulations that may include the types of foods in which it can be used, the maximum amounts to be used, and how it should be identified on food labels.”<sup>262</sup> As

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<sup>256</sup> See Neil Osterweil, “Study: Caffeine May Add Zing to Cola, But It Doesn’t Add Flavor,” WebMD Medical News Archive (Aug. 14, 2000), available at [http://my.webmd.com/article/27/1728\\_60353.htm](http://my.webmd.com/article/27/1728_60353.htm).

<sup>257</sup> See *Id.*: (“Too few people were tested, too little science was used in the testing and too much opinion is contained in the conclusions”).

<sup>258</sup> See generally Mathews, *supra* note 142.

<sup>259</sup> A separate, highly contentious query involves the notion that caffeine is only included in sodas to make them more addictive. In examining the websites of every major soda company, in addition to the website of the National Soft Drink Association, the companies make it uniformly clear that they use caffeine as part of a soda’s “flavor profile.” Therefore, taste experiments like the aforementioned Johns Hopkins study, however methodologically problematic, may attract FDA focus.

<sup>260</sup> In other words, the company must demonstrate that the product is “safe and wholesome.” See generally “The Food and Drug Administration: An Overview,” *supra* note 131.

<sup>261</sup> See e.g. 52 FED. REG. 18,923, 18,925 (1987).

<sup>262</sup> See “How Are Additives Approved for Use in Foods?” *supra* note 160.

applied to Hypo-Cola, this means that the company places caffeine on the list of ingredients, though not necessarily the specific amount used.<sup>263</sup> Once the product is released and marketed for consumer use, FDA officials continue to monitor the level of American consumption of the new additive and the results of any new product safety research; this is to assure that the use of the product continues to be within safe limits.<sup>264</sup> The FDA will take no affirmative steps to ban or further limit caffeine as a food additive so long as the long-term study data continue to show no major harmful effects of its intake.<sup>265</sup>

## 2. Caffeine as a Newly-Proposed Drug

While the food additive approval process may be somewhat more complicated today than it was in the past, “drug development in the United States has undergone many changes in the past 25 years,” and few people “fully realize the complexities involved in developing a new drug.”<sup>266</sup> In fact, the drug development process occurs in several stages:

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<sup>263</sup>Under the current regulatory regime, soft drink companies are not required to list the specific quantities of caffeine used on the products themselves; however, many companies and sources, including the International Food Information Council Foundation and the National Soft Drink Association, publish caffeine content data for interested consumers voluntarily. See e.g. “Caffeine Content of Soft Drinks,” *supra* note 161.

<sup>264</sup>See “How Are Additives Approved for Use in Foods?” *supra* note 160.

<sup>265</sup>See *Id.* The FDA also has several methods of supervising products already in the marketplace, including ARMS: (“In addition, FDA operates an Adverse Reaction Monitoring System (ARMS) to help serve as an ongoing safety check of all additives. The system monitors and investigates all complaints by individuals or their physicians that are believed to be related to specific foods; food and color additives; or vitamin and mineral supplements. The ARMS computerized database helps officials decide whether reported adverse reactions represent a real public health hazard associated with food, so that appropriate action can be taken”).

<sup>266</sup>See Moore, *supra* note 129 at 1244.

Once a promising compound is identified, it must undergo preclinical testing, have an Investigational New Drug Application filed with the U.S. Food and Drug Administration (FDA), and proceed through clinical testing. When sufficient information is gained, a marketing application is filed with the FDA, who identifies it as a New Drug Application for drugs or a Biologics License Application for biologics. After FDA review and approval, postmarketing studies are frequently performed. The FDA and Congress have undertaken several initiatives to expand access and to accelerate drug development and review of investigational drugs for life-threatening and/or serious illnesses. Although the ultimate goal is to bring safer and more effective medical products to patients in a timely manner, multiple challenges face those who participate in drug development.<sup>267</sup>

Of every five-thousand to ten-thousand new drug compounds that will be subjected to the FDA approval process, only an average of one “will proceed through development to Food and Drug Administration approval.”<sup>268</sup>

Further, recent estimates suggest that “developing a new drug requires approximately 10 to 15 years”; this process costs an estimated 897 million dollars.<sup>269</sup> Though the temporal and monetary costs associated with new drug development are high, the FDA has recurring interests in accurate “statistical methods for handling subgroups in the design and analysis of clinical trials,” as well as in “methods to assure data integrity,” such that the agency can be sure that new compounds released to market are safe and effective for human consumption.<sup>270</sup>

Though the FDA admits it has limited knowledge regarding the drug development process, and has many different pressures to weigh when considering the safety of a newly created drug, it is still responsible for creating the standards by which consumer health is protected; this means a more costly and time-consuming

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<sup>268</sup> *See Id.*

<sup>269</sup> *Id.*

<sup>270</sup> *See* Charles Anello, “Emerging and Recurrent Issues in Drug Development,” 18 *STATIST. MED.* 2301, 2301-2309 (1999).

process for drug manufacturers.<sup>271</sup>

In setting standards, FDA functions amid a number of tensions. There is the desire of many people, including much of the academic community, to have more information about a drug before it has been approved. There are special interest groups. . . who want to be represented in studies to attain information specific to them. Consumer protection advocates want to have drugs worked-up well and thoroughly evaluated for safety and efficacy before getting on the market. On the other hand, there are economic pressures to get drugs on the market as soon as possible, and these are highly valid.<sup>272</sup>

With that as the general regulatory backdrop, now assume the existence of a new drug manufacturer, “Hypo-Stim.”

Hypo-Stim has discovered a new methylxanthine compound called caffeine. The company suspects that the drug will be a good mild stimulant, though it may have other potential uses. Hypo-Stim therefore wants to test the product, in hopes that it can eventually garner FDA approval for marketing.<sup>273</sup> The process begins with preclinical research; “after a promising compound is identified, much work occurs before human exposure, usually in vitro and with animal testing.”<sup>274</sup>

The general goal of preclinical research and testing is to weed out potentially dangerous compounds as much as possible prior to human clinical trials, therefore minimizing risk exposure for human test subjects later on.<sup>275</sup> Also, preclinical trials give the drug sponsor or manufacturer the initial opportunity to test whether the new substance will be commercially viable, prior to the FDA having to interrupt production or

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<sup>271</sup> See Janet Woodcock, “An FDA Perspective on the Drug Development Process,” 52 FOOD AND DRUG L. J. 145, 145-150 (1997).

<sup>273</sup> Due to the complexity of the drug approval process, the hypothetical will not explore every aspect of drug approval – space and time prohibit an exhaustive treatment of this subject. The hypothetical is intended only to demonstrate some of the potential concerns the FDA would raise with caffeine if it were a new drug compound seeking approval under the current regulatory regime.

<sup>274</sup> See Moore, *supra* note 129 at 1247.

<sup>275</sup> *Id.* See also Shalala and Woodcock et al., *supra* note 267.

marketing.<sup>276</sup> Preclinical trials involve the use of numerous kinds of studies:

Usual types of studies that are performed include safety pharmacology studies (to assess drug effect on vital organ systems, such as the cardiovascular system, the respiratory system, and the central nervous system), single-dose acute toxicity studies, repeated-dose toxicity studies, local tolerance studies, at least part of the genotoxicity studies (bacterial reverse mutation test and chromosomal damage test), and possibly carcinogenicity studies.<sup>277</sup>

Since caffeine usage has been linked to alterations in central nervous system, cardiovascular system, and (though less so) to respiratory system functioning,<sup>278</sup> Hypo-Stim will likely have to engage in a large battery of expensive preclinical trials, in order to satisfactorily demonstrate that the quantitative effect on those body systems is insufficient to trigger health concerns in humans. Further, caffeine's LD<sub>50</sub> will be recorded in laboratory research; this data will influence whether the company considers going forward with clinical testing.<sup>279</sup>

Though caffeine does stimulate several of the body's major organ systems, study data in the last twenty-five years has shown that these effects are generally mild provided that toxic quantities are not ingested.<sup>280</sup> Therefore, Hypo-Stim can likely proceed out of the preclinical phase and into clinical trials. However, "once the decision is made from preclinical testing that use of the medical product appears promising and clinical testing should proceed," an IND, or Investigational New Drug application, must be filed by the drug's sponsor with the FDA "before research studies begin with a new compound in human subjects."<sup>281</sup> The drug sponsor, in this case Hypo-Stim, is the "person who takes responsibility for and initiates a clinical

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<sup>276</sup> See Woodcock, *supra* note 271.

<sup>278</sup> See generally Goodman & Gilman, *supra* note 4.

<sup>279</sup> See also "Investigational New Drug (IND) Application Process," available at [http://www.fda.gov/cder/regulatory/applications/ind\\_page\\_1.htm](http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm) ("During a drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies").

<sup>280</sup> See e.g. "Wikipedia," *supra* note 6; Brain, *supra* note 14; Goodman & Gilman, *supra* note 4.

<sup>281</sup> Moore, *supra* note 129 at 1247. See also "Investigational New Drug (IND) Application Process," *supra* note 279.

investigation.”<sup>282</sup>

The initiation of the IND process is where the FDA’s regulatory role really begins:

FDA’s role in the development of a new drug begins when the drug’s sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.<sup>283</sup>

This really means that all of Hypo-Stim’s expensive and time-consuming preclinical testing was just to see if the drug could possibly pass initial FDA scrutiny, and undergo later stages of clinical testing.

While the primary purpose of the IND application process is to grant a legal exemption from interstate shipping requirements,<sup>284</sup> a new IND “now consists of multiple sections summarizing the general investigational plan, Investigator’s Brochure (summarizing available safety and efficacy information in animals and humans, when available), protocol(s) for planned studies, chemistry/manufacturing/control information, and pharmacology/toxicology and other information.”<sup>285</sup> Unless the FDA decides to issue a clinical hold on the new drug,<sup>286</sup> “the IND goes into effect and development work may proceed,” though “additional information is then submitted periodically to the IND by the sponsor.”<sup>287</sup> This means that Hypo-Stim’s IND will

<sup>282</sup>21 C.F.R. 312.2(b) (2003), available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.2>.

<sup>284</sup>See *Id.*: (“Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA”).

<sup>285</sup>Moore, *supra* note 129 at 1248.

<sup>286</sup>See 21 C.F.R. 312.42 (2003), available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.42>.

<sup>287</sup>Moore, *supra* note 129 at 1248. Once an IND has been approved, several amendments can be made to the IND under statutory provisions. For example, Protocol Amendments (each new protocol for clinical trials conducted under the U.S. IND)

include detailed summaries of all the caffeine preclinical laboratory findings, LD<sub>50</sub> toxicity data, as well as explanation of caffeine's positive stimulant properties.

Assuming the FDA finds the data sufficient to proceed with clinical trials (barring findings that the drug is either ineffective or unsafe), Hypo-Stim can begin its human scientific investigation in earnest. Clinical approval is likely to occur because caffeine's level of toxicity is very mild when comparing toxic quantities to the amount required to achieve basic stimulant effects. The clinical development work process generally has three distinct phases, the first of which involves somewhere between twenty and eighty "healthy adult volunteers" and requires roughly twelve to eighteen months to complete.<sup>288</sup> The basic rationale of Phase I study is to discover how safe the drug is as increasing dosages are applied and side effects emerge.<sup>289</sup> As applied to Hypo-Stim's caffeine testing, Phase I will likely yield mixed but positive results. It is noted that caffeine causes feelings of alertness at mild dosages, and those effects can be sustained with additional intake; on the other hand, the study data likely reflects possible side effects of nervousness and agitation.<sup>290</sup>

Since the side effects of caffeine are generally mild and often result only at elevated dosages, Phase II studies are likely to follow. Phase II research usually involves one-hundred to three-hundred patients "with the disease or condition under study"; these studies often take more than two years.<sup>291</sup> While this research functions as an additional measure of short-term safety, its primary function is as an effectiveness screen.<sup>292</sup>

For Hypo-Stim, this means that studies are conducted predominantly on sleep-deprived patients, in order to

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must be submitted to the FDA under 21 C.F.R. 312.30. Information Amendments must be submitted regarding any essential information not covered in other reports, subject to 21 C.F.R. 312.31. IND Safety Reports and Annual Reports (21 C.F.R. 312.32 and 312.33, respectively), serve to make the FDA aware of any serious or unexpected adverse events, as well as general progress reports on the development work.

<sup>288</sup>*Id.* at 1249.

<sup>289</sup>*See Id.* In addition to basic dosage and side effect measurements, Phase I generally includes studies of "pharmacokinetic and pharmacologic actions of the drug (absorption, distribution, metabolism, and elimination information)." *Id.*

<sup>290</sup>*See* "Frequently Asked Questions About Caffeine," (Dec. 2001), available at <http://www.coffeefaq.com/caffaq.html>.

<sup>291</sup>Moore, *supra* note 129 at 1249.

<sup>292</sup>*See Id.*

demonstrate caffeine's effectiveness as a wake-up agent.<sup>293</sup> Again, barring unforeseen problems with toxicity or severe side effects, Hypo-Stim can proceed to Phase III.

Research studies in Phase III tend to be the largest and most time consuming; they generally involve thousands of patients, though the number varies depending on the disease or condition under study, and can take upwards of three years to complete.<sup>294</sup> Since more information is already available about the drug at this point, the primary goal is to garner a large sample set with conclusive safety and effectiveness findings in order to proceed with the final stages of FDA approval.<sup>295</sup> Hypo-Stim is unlikely to experience a shortage of available Americans needing a boost in the morning, and is further unlikely to uncover any surprise negative correlations between caffeine intake and human health risk.

The company is therefore ready to proceed with its New Drug Application (NDA); "when the sponsor has collected sufficient information from preclinical and clinical studies to provide the FDA with data for analysis of the safety and efficacy of the study drug, they submit an application for marketing."<sup>296</sup> The NDA process is also very involved; it requires extensive information regarding proposed labeling, manufacturing methods and controls, human drug interaction data, and all relevant preclinical and clinical research information.<sup>297</sup> More importantly, Hypo-Stim will have to provide an "integrated safety summary, an integrated summary of the benefits and risks of the drug, statistical analyses, pediatric information, case report forms and tabulations, patent information, and financial disclosure information."<sup>298</sup> In other words, the company has to have all cards on the table; all information regarding estimated effective dose, side effects, possible dangerous interactions, and necessary warnings must be disclosed so that the FDA can review the drug

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<sup>293</sup>It should be noted that the type of Phase II testing largely depends on the intended purpose or function of the new drug; since caffeine could be widely applied to a variety of medical ailments, this hypothetical is focusing on the stimulant properties only for sake of simplicity.

<sup>294</sup>See Moore, *supra* note 129 at 1249-50.

<sup>295</sup>See *Id.* at 1250.

<sup>296</sup>*Id.*

<sup>297</sup>See *Id.* at 1251.

<sup>298</sup>*Id.*

according to its mandate.<sup>299</sup>

While this hypothetical NDA takes place without the benefit of centuries of safe consumer caffeine use, the new drug will likely be approved, though perhaps with stricter initial labeling requirements and warnings. There is insufficient scientific evidence to support correlations between caffeine and severe health risks; further, though caffeine can cause borderline toxic responses in the occasional individual, the data shows that moderate use (and even heavy use) generally results in only mild side effects.<sup>300</sup> The FDA review process includes “medical, biopharmaceutical, [and] statistical. . . reviews to study and validate the sponsor’s conclusions.”<sup>301</sup> The FDA may request additional research and information if the agency is unsatisfied by the material submitted; it may further perform inspections “to verify the data” and the integrity of “sponsor manufacturing facilities.”<sup>302</sup> The FDA may also consult with an expert review committee, though the findings of the committee are non-binding.<sup>303</sup>

Assuming Hypo-Stim spends the time and money to pass caffeine through the entire FDA review process, a few details remain. The FDA will likely negotiate with Hypo-Stim regarding specific product labeling, but more importantly will decide “whether postmarketing work will be required.”<sup>304</sup>

Once a medical product receives marketing approval, there are several reasons why additional clinical studies may be needed, such as Phase IV commitments required of or agreed to by the sponsor, pharmacoeconomic studies to assess cost/benefit, investigator-initiated studies, and quality-of-life studies.<sup>305</sup>

Assuming caffeine does not require any such reexamination, Hypo-Stim can finally begin to market its drug

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<sup>299</sup> See “Health Information Resource Database,” *supra* note 131, referring to the mission of the FDA to promote safety, effectiveness, and proper labeling.

<sup>300</sup> All previously cited studies in the Paper are incorporated by reference herein.

<sup>301</sup> Moore, *supra* note 129 at 1251.

<sup>302</sup> See *Id.*

<sup>303</sup> See Rados, *supra* note 172.

<sup>304</sup> See Moore, *supra* note 129 at 1251.

to the public, subject to the continued watch of the FDA.

The agency may have concerns about study data reflecting caffeine’s addictiveness; however, the habituation is sufficiently mild that it should not significantly impede the company’s marketing of the new drug. Since there is no known serious problem with caffeine use in moderate doses, any additional concerns the FDA has can be addressed through product labeling and FDA Guidances. If long-term health study data continues to be generally favorable, caffeine will continue to be approved for use as a valid drug product.

#### **V. Conclusion: Caffeine – The New and Improved American Crutch**

The hypothetical food additive and drug discussions are not meant to supercede a sensible policy of moderated intake.<sup>306</sup> To paraphrase an old American saying, “too much of a good thing can be bad for your health.” This statement is valid with regard to almost anything, and caffeine intake is probably no exception. Though the FDA cannot absolutely guarantee that every consumer will exercise moderation of caffeine intake, the same could be said for any widely available food and over-the-counter drug product.

Fortunately, the FDA arguably has much less to worry about with regard to caffeine regulation nowadays than it did in 1980 when negative caffeine correlations were first being asserted. The majority of medical

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<sup>306</sup>One source summarizes the rationales for the FDA review processes as follows: (“In the U.S., the review of a new drug application serves many purposes. It is a public scientific document reflecting how a regulatory agency interprets information submitted for market approval of a drug. It provides a public record which needs to be ‘correct, coherent, well-organized, and credible’. It also shows the scientific aspects of the review. The goal of an application review is to determine if the data submitted supports proposed labeling claims and whether or not there is substantial evidence of efficacy and evidence that the drug is safe”). Anello, *supra* note 270. Since caffeine arguably satisfies all of these ideas, there is no significant reason to assume it is unworthy of current levels of consumer intake.

studies conducted in the intervening period generally tend to demonstrate that moderate use of caffeine, both in foods and in drugs, poses no significant health risks to most consumers, representing a turnaround from earlier findings. Further, research is beginning to show (with gradually increasing levels of persuasiveness) that caffeine intake at varying higher levels is linked to a number of potential health benefits.

While it is admittedly too early to assume that a heavy daily intake of “Starbucks” will help prevent the onset of diseases such as Parkinson’s and type-2 diabetes, the FDA cannot ignore the positive correlations being drawn between caffeine consumption and human health. More importantly, given the demanding amount of time and money required to supervise the creation of new food additives and drugs, the FDA need not waste additional precious regulatory resources on a substance that has been safely ingested for hundreds, if not thousands of years. There is no additional need for FDA regulation of caffeine with respect to food or drug products.