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DIETARY SUPPLEMENTS

Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids

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Chairman
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Ranking Minority Member
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The dietary supplement industry estimates that as many as 2 billion doses of dietary supplements containing botanical ephedrine alkaloids are consumed each year in the United States. The principal source of botanical ephedrine alkaloids is the Chinese herb *ma huang*. Traditionally, this substance was used by Chinese physicians to treat conditions such as hay fever and asthma. In Western medicine, synthetic ephedrine alkaloids have been used in products such as over-the-counter asthma and cold medicines, while botanical ephedrine alkaloids have been used in dietary supplements that are promoted to provide health benefits, including helping individuals lose weight and increase energy levels.

In June 1997, the Food and Drug Administration (FDA) published a proposed rule that would establish a dosing regimen, require warning statements, and affect other aspects of product labeling for dietary supplements containing ephedrine alkaloids. FDA developed its proposed rule in response to what it termed "serious illnesses and injuries, including multiple deaths, associated with the use of dietary supplement products that contain ephedrine alkaloids." FDA based its rule, in part, on a number of adverse events reports (AER) it received that indicated that some health problems could have been associated with use of dietary supplements containing ephedrine alkaloids.

FDA determined that its proposed rule on dietary supplements containing ephedrine alkaloids was an economically significant rule and, therefore, was required to conduct a cost-benefit analysis pursuant to the requirements in Executive Order 12866.[1] Other regulatory analysis requirements for federal rulemaking are those under the Regulatory Flexibility Act (RFA), which directs agencies to consider the potential impact of regulation on small businesses and other small entities,[2] and the Unfunded Mandates Reform Act (UMRA), which generally requires agencies

[1]E.O. 12866 was issued on September 30, 1993, and covers all agencies except independent regulatory agencies.

[2]5 U.S.C. 601-612.

to prepare cost-benefit analyses for any proposed regulation that would impose mandates likely to result in expenditures of $100 million or more in any 1 year.[3]

Industry groups and the Small Business Administration's (SBA) Office of Advocacy have challenged FDA's proposed rule, claiming that the scientific information and AERs supporting the rule were poor and unreliable. Further, industry groups and the Office of Advocacy claimed that the cost-benefit analysis performed by FDA understated the costs of the regulation and overestimated the benefits. They also had concerns about compliance with RFA's and UMRA's procedural requirements.

In light of the concerns expressed by SBA and industry groups, you asked us to examine (1) the scientific basis for FDA's proposed rule and (2) the agency's adherence to the regulatory analysis requirements for federal rulemaking. In examining the basis for the rule, you asked that we examine scientific evidence, FDA's past use of and internal guidance on AERs in rulemaking, and information contained in the AERs for determining dosing regimens and benefits that would arise from the proposed rule. Regarding the rulemaking requirements, you asked that we determine the extent to which FDA's analysis contained elements expected in a federal agency's cost-benefit analysis and to analyze FDA's compliance with the requirements in RFA and UMRA.

To meet these objectives, we interviewed representatives of and obtained documents from FDA, SBA's Office of Advocacy, the Office of Information and Regulatory Affairs (OIRA) in the Office of Management and Budget (OMB), and the dietary supplement industry. We also examined the public docket of the proposed rule, performed a content analysis of a random sample of AERs, and reviewed scientific literature and case reports of adverse events from products containing ephedrine alkaloids. We conducted our review from September 1998 to May 1999 in accordance with generally accepted government auditing standards. (See app. I for further information on our scope and methodology.)

Results in Brief

FDA based its proposed rule on numerous reports of adverse events associated with products thought to contain ephedrine alkaloids; it also used evidence from scientific literature indicating that ingestion of ephedrine alkaloids adversely affects some individuals. The number and type of AERs warranted FDA's consideration of steps to address safety

[3]2 U.S.C. 638 and 1532.

issues. However, we have concerns about the strength of some of the information FDA used to support two aspects of the proposed rule: the dosing level and duration of use limits. While there was scientific evidence showing adverse events at levels above 20 mg per serving, FDA's dosing level proposal of 8 mg per serving was based on information associated with only 13 AERS—the quality of which is questionable. For the duration of use limits, FDA relied on scientific studies that showed problems associated with extended use, well beyond the 7-day limit proposed. Moreover, FDA did not establish a causal link between the ingestion of ephedrine alkaloids and the occurrence of adverse events for either its proposed dosing level or duration of use. FDA also based its estimate of the benefits of the proposed rule on the annual number of adverse events reported to FDA. However, because FDA did not document which AERS it identified as containing "serious" events, we could not determine the accuracy of FDA's estimated benefits. In addition, FDA has no internal guidance on the use of AERS for rulemaking related to foods and dietary supplements, and the AERS were used differently in this proposed rule than in prior rulemaking.

The agency generally complied with the statutory and executive order requirements for rulemaking, but the cost-benefit analysis that accompanied the rule does not reflect the full range of uncertainty associated with the proposed rule. FDA's cost-benefit analysis and other analyses included the primary elements required under E.O. 12866 and related "best practices" guidance and RFA. UMRA's requirements did not appear to apply to the rule. Although FDA disclosed the basic methodology, data, and assumptions used in its cost-benefit analysis, the agency did not always disclose why certain key assumptions were made or the degree of uncertainty involved in those assumptions. It also did not disclose that alternative assumptions would have had a dramatic effect on the agency's estimate of the benefits of the proposed actions.

While FDA's conclusions regarding the desirability of the proposed action may be valid, we believe these conclusions are open to question because of limitations and uncertainties associated with the agency's scientific and economic analyses. Given these uncertainties, we recommend that FDA obtain additional information to support the proposed dosing levels and duration of use limits and improve the transparency of its cost-benefit analysis before proceeding to final rulemaking.

Background

FDA is responsible for overseeing the federal government's regulation of drugs, medical devices, food safety, veterinary medicine, and biological products. Unlike many of these products, dietary supplements do not have to undergo preapproval by FDA to determine their safety or efficacy. The Dietary Supplement Health and Education Act of 1994 created a new framework for FDA's regulation of dietary supplements as part of its oversight of food safety.[4] The act allows dietary supplement products to bear a statement describing how consumption of the supplement can affect humans,[5] but manufacturers of dietary supplements cannot make a drug claim for the product—that is, a statement claiming to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases.[6]

Dietary supplements containing botanical sources of ephedrine alkaloids are currently marketed for weight loss and increased energy. These products are marketed in a variety of forms, including pills, powders, liquid drops, and teas. Currently, FDA has no requirements that the packages for these products include dosing regimens and warning labels.

Over-the-counter products containing synthetic ephedrine alkaloids are considered safe and effective for people ages 12 and older to temporarily relieve shortness of breath, tightness of chest, and wheezing due to bronchial asthma, if recommended dosages are followed. The recommended dosages—which range from 12.5 mg to 25 mg every 4 hours, not to exceed 150 mg per day—are provided on the label. Labels for over-the-counter drug products containing ephedrine alkaloids list side effects, such as nervousness, sleeplessness, nausea, and loss of appetite. The labels also warn against using the product if, for example, the potential user has high blood pressure, heart disease, thyroid disease, or diabetes, or has been hospitalized for asthma or is taking a prescription drug for asthma, unless directed by a doctor. Labels also note that if symptoms persist or become worse, users should discontinue taking the drug and consult a doctor. After reports of stroke in asthmatics who had taken ephedrine along with prescription monoamine oxidase inhibitors,[7] precautions against using both drugs concurrently were added to the label.

[4]P.L. 103-417.

[5]Such statements may (1) claim a benefit related to a classical nutritional deficiency disease, (2) describe the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, (3) characterize the documented mechanism by which the ingredient acts to maintain such structure or function, or (4) describe general well-being from the consumption of the ingredient.

[6]21 U.S.C. 321 (g)(1).

[7]Monoamine oxidase inhibitors are drugs used to treat depression, psychiatric or emotional conditions, or Parkinson's disease.

FDA has no authority to require submission of reports of adverse events. FDA must generally rely on consumers or their friends and family members, physicians or other health care professionals, product manufacturers, and state health agencies to voluntarily report adverse events. FDA uses these AERs as a passive monitoring tool to identify potentially serious public health issues that may be associated with the use of a particular product or type of products. Like all passive surveillance systems, AERs have certain limitations such as underreporting and poor report quality (see app. II for a further discussion of the adverse event monitoring system).

FDA's Proposed Rule on Ephedrine Alkaloids

FDA's analysis of AERs and information from the scientific literature relating to ephedrine alkaloids indicated to the agency that there was cause for concern regarding a potential public health problem associated with dietary supplements containing ephedrine alkaloids. At the time of the proposed rule, FDA had received over 800 AERs for products thought to contain ephedrine alkaloids—more AERs than the agency had received for any other dietary supplements.

According to agency officials, FDA found that, unlike most AERs related to foods, the AERs relating to ephedrine alkaloids commonly involved visits to a physician or emergency room. Some of these reports were very serious, including effects such as strokes, and the events were occurring in a population of young adults in which such serious events are not expected. FDA officials also stated that the adverse physiological and pharmacological effects from dietary supplements believed to contain botanical sources of ephedrine alkaloids were similar to those reported for drugs containing synthetic sources of ephedrine alkaloids, but these effects were being seen at lower doses and potencies for botanicals than in the drug products.

From 1994 through 1997, FDA took a series of steps to respond to what it perceived was a public health concern related to these products. In 1994, FDA's Center for Food Safety and Applied Nutrition (CFSAN), which oversees dietary supplements, issued a medical bulletin outlining potential adverse reactions from dietary supplements containing ephedrine alkaloids. The agency issued a press release warning consumers not to purchase a particular brand of dietary supplement containing ephedrine alkaloids that the agency determined could cause severe injury or death in some people.

In October 1995, FDA convened a special work group composed of pharmacologists, physicians, and industry representatives to address concerns related to the use of dietary supplements containing ephedrine alkaloids, but no consensus developed on how to address the public health concerns outlined by FDA. In August 1996, FDA's Food Advisory Committee was asked to provide opinions on and rationale for specific ways to address problems associated with dietary supplements containing ephedrine alkaloids. Over half the committee members concluded that no safe level for ephedrine alkaloids could be identified and recommended that these products be removed from the market. Most of the other members felt that a fairly low level of ephedrine alkaloids would be "reasonably safe." The Food Advisory Committee was unable to identify a benefit for ephedrine alkaloids in terms of supplementing the diet.

In June 1997, FDA published a proposed rule regarding dietary supplements containing ephedrine alkaloids.[8] In two subsequent notices the agency reopened and extended the comment period on the proposed rule until December 1997.[9] The proposed rule

- defines levels of the amount of ephedrine alkaloids in a serving of dietary supplements at and above which the product would be deemed adulterated (8 mg),
- places restrictions on the frequency of use and daily dosages (24 mg or more),
- requires that labels on these supplements contain a statement warning that the product should not be used for more than 7 days,
- prohibits the use of ephedrine alkaloids with ingredients that have a known stimulant effect (for example, caffeine),
- prohibits certain labeling claims that require long-term intake of the supplements to achieve the purported purpose,
- requires a warning statement in conjunction with claims that encourage short-term excessive intake, and
- requires a specific warning statement to appear on product labels.

Federal Regulatory Analysis Requirements

E.O. 12866 establishes certain rulemaking responsibilities for covered agencies. Among other things, the order states that, in deciding whether and how to regulate, agencies should assess all costs and benefits of available regulatory alternatives, including both quantifiable and qualitative effects. The order also states that, in choosing among

[8]62 Fed. Reg. 30678.

[9]62 Fed. Reg. 44247 and 62 Fed. Reg. 48968.

alternatives, an agency should select those approaches that maximize net benefits and "base its decisions on the best reasonably obtainable scientific, technical, economic, and other information concerning the need for, and consequences of, the intended regulation." The order requires agencies to conduct cost-benefit analyses for all regulatory actions that are likely to result in a $100 million annual effect on the economy or are otherwise economically significant. In January 1996, the Administrator of OIRA issued "best practices" guidance on preparing cost-benefit analyses under the order. The guidance indicates that an analysis should contain certain basic elements and should be "transparent"—disclosing how the analysis was conducted, what assumptions were used, and the implications of plausible alternative assumptions.

During the past 20 years, the Congress has attempted to improve the federal rulemaking process by enacting a number of statutes that impose certain analytical requirements on agencies issuing proposed regulations. For example, RFA of 1980 was enacted in response to concerns about the effect that federal regulations could have on small entities. RFA directs all agencies to give particular attention to the potential impact of regulation on small businesses and other small entities and requires consideration of regulatory alternatives that are less burdensome to small entities. Under RFA, an agency must prepare an initial regulatory flexibility analysis at the time proposed rules are issued unless the head of the agency determines that the proposed rule would not have a "significant economic impact upon a substantial number of small entities." The act also requires agencies to ensure that small entities have an opportunity to participate in the rulemaking process.

Other statutory rulemaking requirements are set forth in UMRA. UMRA generally requires agencies (other than independent regulatory agencies) to prepare cost-benefit and other analyses for any regulations imposing mandates that are likely to result in expenditures of $100 million or more in any 1 year either by state, local, and tribal governments, in the aggregate, or by the private sector. Although UMRA's scope and requirements differ from E.O. 12866, the provisions on economic analysis are very similar. Accordingly, the guidance for implementing the executive order states that the economic analysis that the agency prepares should also satisfy the requirements of UMRA.

FDA Analyses Relied on Poorly Documented Reports of Adverse Events

To develop its proposed rule, FDA used a combination of scientific evidence on the effects of ephedrine alkaloids and a set of reports it received on adverse events associated with dietary supplements containing ephedrine alkaloids. While the signs and symptoms described in the AERs were consistent with available scientific evidence and known physiologic and pharmacologic effects of ephedrine alkaloids, the AERs were poorly documented. FDA also used the AERs differently than in its past rulemaking. Specifically, the agency used AERs as the sole source of support for specific dosing levels, relied on weak information to set limits on duration of use, and did not perform a causal analysis to determine whether ingestion of a dietary supplement containing ephedrine alkaloids caused or contributed to the adverse events. FDA also used these AERs to determine the number of serious events that could be attributed to the dietary supplements and the expected benefits that would arise if the proposed rule were implemented. However, FDA did not document which AERs it determined to be serious. Moreover, it did not establish criteria to determine which events were serious and did not perform any reliability assessments of its analyses.

Scientific Information Indicates Ephedrine Alkaloids Can Affect the Cardiovascular and Nervous Systems

Our review of the scientific literature found case reports that suggested that ephedrine alkaloids could increase blood pressure in persons with normal and high blood pressure;[10] predispose certain individuals to tachycardia (rapid heart rate);[11] and cause cardiomyopathy (disease of the heart muscle),[12] stroke,[13] or myocardial necrosis (death of cells in the heart).[14] We also found descriptions of adverse events associated with

[10]S. Chua and S. Benrimoj, "Non-Prescription Sympathomimetic Agents and Hypertension," Medical Toxicology, Vol. 3 (1988), pp. 387-417.

[11]D. McCleave and others, "Compartmental Shift of Potassium—A Result of Sympathomimetic Overdose," Australian and New Zealand Journal of Medicine, Vol. 8 (1978), pp. 180-83.

[12]J. Gualtieri and C. Harris, "Dilated Cardiomyopathy in a Heavy Ephedrine Abuser," (abstract) Journal of Toxicology, Clinical Toxicology, Vol. 34 (1996), pp. 581-82.

[13]A. Bruno and others, "Stroke Associated With Ephedrine Use," Neurology, Vol. 43 (1993), pp. 1313-16.

[14]P. Pentel and others, "Myocardial Necrosis Due to Intraperitoneal Administration of Phenylpropanolamine in Rats," Fundamental and Applied Toxicology, Vol. 9 (1987), pp. 167-72.

ephedrine alkaloids that affected the central nervous system, such as mania,[15] paranoid psychoses,[16] and seizures.[17]

Our review found only one clinical study examining the effects of a botanical source of ephedrine alkaloids, *ma huang*, on heart rate and blood pressure. The study of adults with normal blood pressure found a statistically—but not clinically—significant increase in heart rate but variable effects on blood pressure.[18] However, "in combination with other stimulants and at higher doses, effects of magnification of the heart rate and blood pressure response could be expected." One report also highlighted a case of mania as a result of ingestion of a dietary supplement containing *ma huang*.[19]

We also reviewed a number of studies using clinical trials that evaluated the efficacy of ephedrine (a synthetic ephedrine alkaloid)—alone or in combination with caffeine—for weight loss. Although these trials were not designed to determine whether ephedrine is safe to use during weight loss programs, FDA concluded that this body of literature showed "clinically significant adverse effects in populations with no known risk factors with the use of ephedrine and that synergistic adverse effects can result when ephedrine and caffeine are combined." FDA further concluded that "The patterns and types of the adverse effects reported in these trials are consistent with the known effects of sympathomimetic agents[20]—that is, they mainly involved nervous and cardiovascular system effects."

AERs Were Used Differently for Developing the Proposed Rule Than for Prior Rulemaking

To develop FDA's proposed rule on dietary supplements containing ephedrine alkaloids, CFSAN used AERs differently than in prior FDA rulemaking. FDA officials acknowledge that the agency does not have any formal internal guidelines on the use of AERs for rulemaking and provided five examples of past rulemaking in which CFSAN used several sources of information in addition to AERs to support the agency's proposals. For the

[15]W. Clovis, "Mania and Cough Syrup," Journal of Clinical Psychiatry, Vol. 54 (1993), p. 200.

[16]M. T. Lambert, "Paranoid Psychoses After Abuse of Proprietary Cold Remedies," British Journal of Psychiatry, Vol. 151 (1987), pp. 548-50.

[17]S. M. Mueller and E. B. Solow, "Seizures Associated With a New Combination Pick-Me-Up Pill," Annals of Neurology, Vol. 11 (1982), p. 322.

[18]L. White and others, "Pharmacokinetics and Cardiovascular Effects of Ma-huang (Ephedra sinica) in Normotensive Adults," Journal of Clinical Pharmacology, Vol. 37 (1997), pp. 116-22.

[19]R. R. Capwell, "Ephedrine-Induced Mania From an Herbal Diet Supplement" (letter), American Journal of Psychiatry, Vol. 152 (1995), p. 647.

[20]Such agents produce physiological responses resembling those that are caused by the action of the sympathetic nervous system, as in tending to reduce digestive secretions and speeding up the heart.

proposed rule on dietary supplements containing ephedrine alkaloids, CFSAN used AERs alone to determine specific dosing levels.[21]

In a prior rulemaking, FDA used prevalence estimates among people with asthma to determine sensitive populations who might be affected by sulfiting agents[22] and convened a scientific panel to examine exposure estimates and evidence from clinical experiments.[23] For its rulemaking on protein supplements, FDA used data collected through a telephone survey, conducted jointly with the Centers for Disease Control and Prevention (CDC), and information on death rates from the National Center for Health Statistics. FDA also initiated its own experimental protocols to examine the basic metabolic mechanisms of protein diets.[24] FDA's proposed rule on supplements and drugs containing iron relied on data from the American Association of Poison Control Centers and the U.S. Consumer Product Safety Commission to determine fatalities from accidental iron poisonings. Data from the National Electronic Injury Surveillance System were also incorporated to estimate the number of cases of hospital emergency room treatment for iron ingestion.[25] FDA did not establish dosing levels in any of these rulemakings.

Although AERs were used as early warning signals in many of these cases, the proposed rule on ephedrine alkaloids relied more heavily on AERs than did prior rulemaking efforts. (See app. III for additional information on the use of AERs in prior rulemaking.)

Shortcomings of AERs and FDA's Reliance on Them Add Uncertainty to FDA's Proposed Rule

The inherent weaknesses of AERs—along with FDA's heavy reliance on them—lead to uncertainty regarding the dosing regimen outlined in the proposed rule. The AERs used in the rule lacked or had inconsistent information relevant to FDA's analysis, such as the amount of product used, how often it was used, or for how long it was used. The limitations of a passive surveillance system such as AERs call into question FDA's ability to

[21]FDA also used AERs to show evidence of dechallenge (signs and symptoms resolve or improve when a consumer stops using a product) and rechallenge (symptoms recur when the consumer resumes using the product).

[22]Sulfiting agents are one type of chemical preservative that serves to prevent or to delay the process of browning and deterioration of raw fruits and vegetables.

[23]51 Fed. Reg. 25021.

[24]49 Fed. Reg. 13679.

[25]62 Fed. Reg. 2218.

determine a specific dosing level based solely on these reports.[26] FDA did not perform a causal analysis to determine if, in fact, the 13 AERs it used to set dosing levels were caused by supplements containing ephedrine alkaloids. FDA indicated in the proposed rule that 10 to 73 percent of reported adverse events might not be related to consumption of dietary supplements containing ephedrine alkaloids. FDA's support for its recommended limit on duration of use was also weak.

FDA's lack of documentation on which adverse events it classified as serious makes it difficult to determine the validity of FDA's estimates of the benefits that would arise from the proposed rule. In addition, FDA did not have specific criteria to determine which events should be considered serious and did not perform a reliability assessment to ascertain the validity of its estimates of serious events.

Adverse Event Reports Were Incomplete and Inconsistent

Prior to the proposed rulemaking, FDA received 864 AERs on dietary supplements containing ephedrine alkaloids—more AERs than for any other single dietary supplement. However, the AERs that we examined often lacked important information, and the information that they did contain was sometimes inconsistent. These problems suggest that AERs should be used with caution, and their use can contribute to uncertainty in FDA's conclusions.

In examining a random sample of the AERs (92 out of 864 reports), we found that 39 percent lacked information on the amount of product consumed, 41 percent lacked information on the frequency with which the product was consumed, and 28 percent lacked information on the duration for which the product was consumed. A total of 45 percent of the AERs lacked information on either dose, frequency, or duration, and 24 percent lacked information on all three dimensions. Finally, 62 percent of the AERs in our sample did not contain medical records, which are important in determining potential underlying conditions that might have caused the adverse event (rather than assuming ingestion of dietary supplements containing ephedrine alkaloids caused the event).

We also found cases where the amount of product consumed or the duration for which it was consumed was listed differently in multiple locations within an AER. In addition, the name of the product consumed sometimes varied within an AER. As a result, it is difficult to identify the

[26]FDA evaluated the scientific literature to determine that ephedrine alkaloids could pose hazards at 20 mg per dose. However, FDA relied solely on AERs in setting a specific dose level of 8 mg per dose and 24 mg per day.

correct information that corresponds to the event being reported and to make inferences from such reports.[27]

FDA Relied Solely on AERs for Setting Specific Dosing Regimens and Did Not Determine If These Events Were Caused by Ephedrine Alkaloids

In its proposed rule, FDA concluded that one possible strategy for addressing these adverse events was to restrict the level of ephedrine alkaloids in dietary supplements. To determine a possible dosing level, FDA reviewed clinical trials on therapeutic uses for ephedrine alkaloids used alone and in combination with other pharmaceutical substances to treat obesity. These trials indicated that 20 mg ephedrine alkaloids per dose could cause adverse events to occur in the subjects taking part in the clinical trial.[28] Thus, FDA concluded that 20 mg per serving of ephedrine alkaloids presented potential risks for some individuals.

However, the studies did not provide information on risk at levels below 20 mg per serving for use in the general population, and lean or moderately overweight persons have been shown to be more sensitive to substances like ephedrine alkaloids than are obese individuals. To determine if serious adverse events were occurring at levels below 20 mg per serving, FDA obtained and tested the dietary supplement products associated with AERs that were serious, where available.[29] FDA then identified the levels of ephedrine alkaloids in those AERs by performing laboratory analyses of ephedrine alkaloid levels for dietary supplements turned over to the agency by the consumers who suffered adverse events (consumer samples). FDA also performed tests on samples obtained from the marketplace for situations in which the consumer experiencing the adverse event no longer possessed the product (consumer-related samples). In all, from more than 800 AERs submitted to the agency between 1993 and the time of the proposed rule, FDA collected and tested 34 samples of consumer or consumer-related products.

From the 34 samples tested, 13 product samples met two criteria: the results of the analytical tests were valid and supportable and the products contained less than 20 mg of ephedrine alkaloids. FDA then set a specific dosing level of 8 mg per serving. In other words, FDA relied on these 13 AERs where the products tested yielded ephedrine alkaloid levels below 20 mg per serving as the sole source of support for the specific dosing level

[27]While these types of problems do not occur uniquely among reports involving ephedrine alkaloids, they reinforce the fact that there are inherent weaknesses of passive surveillance systems such as AERs.

[28]See, for example, A. Astrup and others, "The Effect and Safety of an Ephedrine/Caffeine Compound Compared to Ephedrine, Caffeine and Placebo in Obese Subjects on an Energy Restricted Diet. A Double Blind Trial," International Journal of Obesity, Vol. 16 (1992), pp. 269-77.

[29]Testing was necessary because there are no requirements that product contents be labeled.

found in the proposed rule.[30] Table 1 provides information on these 13 cases.

Table 1: Summary of 13 AERs Used for Specific Dosing Level

	Total ephedrine alkaloids (mg)[a]			
AER number	**Initial**	**Recheck**	**Type of sample**	**Symptoms as described in AER**
10088	1.6	2.0	Consumer	Elevated blood pressure, severe headache, nausea, heavy perspiration, passed out
11233	1.8	Trace	Consumer	Hair loss, sleeplessness, chest pain, increased energy
11106	Trace	1.9	Consumer	Sweating, trembling, high blood pressure, menstrual bleeding, suffered stroke
9754	8.8	8.8	Consumer	Heat stroke, chest and back pain, rapid heart rate, hyperthermia
8475	9.1	9.9	Consumer-related	Tremors, tics, insomnia, hyperactive reflexes
10974	11.0	13.1	Consumer-related	Seizure
11144[b]	10.0, 11.7	9.0, 15.3	Consumer-related	Transient amnesia, lost consciousness
10946	10.5	8.3	Consumer	Rash, increased blood pressure
9751	9.2	11.1	Consumer	Attempted suicide
10919	11.2	14.4	Consumer	Weakness, dizziness, elevated blood pressure
11134[c]	14.8		Consumer	Death
11619	15.1	18.5	Consumer	Rapid heart rate, headache, numbness, face droop, dizziness
11298	16.6	20.6	Consumer	Blood in urine, elevated blood pressure

[a]Levels are based on the amount the consumer reported having used per serving. Where consumer intake was unknown, the levels were based on the label directions for use. FDA performed an initial analysis and a recheck analysis for the samples it obtained.

[b]Two consumer-related samples were tested.

[c]Recheck analysis was not conducted because original analysis was performed by a national or international expert.

While FDA used these 13 AERs to set a dosing level, the agency did not perform a causal analysis to determine whether the reported events were, in fact, caused by the ingestion of dietary supplements containing ephedrine alkaloids. Our review of these 13 AERs found numerous problems that raise questions about the causal relationship between ingestion of the implicated product and the adverse events observed. For example,

[30]FDA's laboratory analysis of the ephedrine alkaloid levels in the 34 AERs showed levels from approximately 1 to 50 mg per serving. According to FDA, these reports show a pattern of clinically significant adverse events at levels approaching and above 10 mg. Given the variability in the testing procedure and natural variability in the alkaloid content of botanical ingredients, FDA determined a range around 10 mg per serving could be expected to deviate by 10 to 20 percent. From this, FDA tentatively concluded that an 8 mg limit per serving could be associated with a serious adverse event.

- three AERs included physician reports that stated the cause of the event was not related to a dietary supplement;
- one consumer-related sample was obtained and tested 2 years after the initial event, and possible reformulations of the product might have resulted in different levels of ephedrine than the product implicated in the reported adverse event;
- three individuals reporting adverse events had experienced similar problems prior to or well after using the dietary supplement;
- one individual who experienced the event was eating only one meal a day; and
- one AER contained no medical records.

Some of the 13 AERs had more than one of these problems. As a result, there are uncertainties in FDA's conclusions in setting a specific dosing limit since this limit was based on a small number of adverse events—events which may or may not have been a result of ingestion of dietary supplements containing ephedrine alkaloids.

Weak Support for FDA's Proposed Limitation on Duration of Use

In its proposed rule, FDA also recommended a 7-day limit on the use of dietary supplements containing ephedrine alkaloids. FDA used the recommendations of some members from its special work group and Food Advisory Committee, scientific literature, and data from the AERs to support this limit. However, we found several weaknesses in FDA's evidence.

First, FDA did not present scientific evidence specifically pointing to an increase in adverse events beginning at 7 days and under normal use conditions. Rather, the scientific information FDA used to support a 7-day limit outlined problems associated with extended use (months and years) of ephedrine alkaloids. The agency also cited support for its 7-day limit from studies involving other sympathomimetic agents, such as cocaine and methamphetamines, but these studies also involved long-term use of the drug. Second, FDA did not demonstrate a causal relationship between ingestion of dietary supplements containing ephedrine alkaloids and adverse events reported to the agency. Since FDA indicated in the proposed rule that 10 to 73 percent of the reported adverse events might not be related to consumption of dietary supplements containing ephedrine alkaloids, the use of the AERs to describe a pattern of response across time

is questionable.[31] Finally, the agency did not demonstrate the relationship between both dose levels and frequency of ingestion and duration of use. As a result, there are uncertainties in the agency's analysis of the relationship between duration of use of dietary supplements containing ephedrine alkaloids and the occurrence of adverse events.

FDA Based Its Risk Reduction Value on Poorly Documented Estimates of Serious Adverse Events

FDA noted in the proposed rule that there were an average of 174 adverse events reported each year between January 1993 and June 1996 and that 81 were serious events. FDA divided the serious adverse events into five categories and outlined examples for each type: (1) cardiovascular (dysrhythmia or abnormal heart rhythms, severe hypertension, cardiac arrest, heart attack, angina, myocardial infarction, stroke, and cardiomyopathy or muscle damage to heart); (2) central nervous system (psychosis, suicide or attempted suicide, altered or loss of consciousness or disorientation or confusion, seizure, mania, and severe depression); (3) liver damage or hepatitis; (4) death; and (5) other events (vestibular or inner ear disturbances, altered serum enzymes, myopathies or muscle disease, genitourinary system disturbances or urinary tract problems, prostate problems, and dermatological syndromes or rashes).

However, FDA did not record which AERs it considered to be serious. FDA officials stated that a count had been performed by medical doctors of the agency on the number of serious events, but there was no record of the specific cases that they had identified as serious events. In addition, rather than providing AER reviewers a standard definition, FDA told them to use their clinical judgment in determining what they considered a serious event.[32] Also, FDA did not perform any assessments of interrater reliability among reviewers to ensure that their judgments were consistent.

Based on the yearly average of serious adverse events reported to FDA from January 1993 to June 1996, FDA estimated an annual value of risk reduction that would occur as a result of the proposed actions outlined in the rule. However, because FDA did not record which AERs were deemed

[31]FDA pointed out in the proposed rule that the relationship of the reported adverse event to the consumption of dietary supplements categorized as containing ephedrine alkaloids had been corroborated in about 27 percent of cases where a consumer stopped taking a product and the symptoms improved. FDA also noted that a certain number of false reports might also be expected. Thus, they believed that the actual percentage of cases related to consumption of ephedrine alkaloids was between 27 percent and 90 percent. FDA's professional judgment was that 80 percent of the reported cases were actually related to consumption of dietary supplements containing ephedrine alkaloids.

[32]FDA noted that the medical doctors were well qualified—by training and experience—to make decisions regarding the clinical significance of the event.

serious, we could not determine the accuracy of FDA's conclusions regarding the actual benefits that would arise from the proposed rule.

FDA's Analysis of Impacts Generally Adhered to Rulemaking Requirements but Was Not Fully Transparent

FDA generally complied with executive order and statutory requirements for rulemaking. It prepared a cost-benefit analysis containing the basic elements expected for an economically significant rule under E.O. 12866. It also prepared an initial regulatory flexibility analysis and provided opportunities for small businesses to participate in the rulemaking process, as required by RFA. FDA's analysis of impacts would also likely satisfy most, if not all, of the analytical requirements of UMRA, although its proposed rule does not appear to trigger these requirements.

However, OIRA's guidance on preparing cost-benefit analyses under E.O. 12866 states that an agency's analysis must be "transparent"—that is, disclose how the analyses were conducted and what assumptions were used. FDA's analysis was only partially transparent. Although FDA described its key assumptions and identified substantial uncertainties regarding the data supporting its proposed rule, it did not fully disclose why certain key assumptions were made, the degree of uncertainty involved in those assumptions, or that alternative assumptions would have had a dramatic effect on the agency's estimates of the costs and benefits of the proposed regulatory actions. Because of these uncertainties and limitations, the results of FDA's analysis are still open to question.

FDA's Analysis Addressed the Basic Cost-Benefit Elements but Was Only Partially Transparent

Under E.O. 12866, agencies are required to conduct cost-benefit analyses for all regulatory actions that are likely to result in a $100 million annual effect on the economy or are otherwise economically significant. OIRA's "best practices" guidance states that a federal agency's cost-benefit analysis should contain three basic elements: (1) a statement of the need for the proposed action, (2) an examination of alternative approaches, and (3) an analysis of benefits and costs. Although the guidance provides for flexibility and professional judgment in conducting the analysis, it establishes a clear expectation that the analysis of the risks, benefits, and costs associated with the regulation "must be guided by the principles of full disclosure and transparency." For example, the guidance says the analysis should identify and explain the data or studies on which the estimates of benefits and costs are based "with enough detail to permit independent assessment and verification of the results." The guidance also states "where benefit or cost estimates are heavily dependent on certain assumptions, it is essential to make those assumptions explicit

and, where alternative assumptions are plausible, to carry out sensitivity analyses based on the alternative assumptions."[33] (See app. IV for a more detailed discussion of the analytical requirements under E.O. 12866 and related guidance, as well as our assessment of FDA's cost-benefit analysis in terms of that guidance.)

FDA's cost-benefit analysis contained the three basic elements stipulated in the guidance, but certain other specific elements in the guidance appear to be lacking:

- With regard to the first element, FDA stated that the proposed rule was needed because of a significant market failure—specifically, inadequate consumer information on the health risks associated with dietary supplements containing ephedrine alkaloids. However, the OIRA guidance indicates that even where a market failure exists, agencies should also discuss the appropriateness of alternatives to federal regulation, such as state or local regulation. FDA's analysis did not recognize efforts in several states to regulate these products or say why federal regulation was a better approach.
- For the second element, FDA discussed seven regulatory options, including (1) a baseline alternative of taking no action, (2) taking no action but generating additional information, (3) taking the proposed action, (4) taking the proposed action but allowing a higher potency limit for the supplements, (5) banning dietary supplements that contain ephedrine alkaloids, (6) taking the proposed action but not requiring the warning statement, and (7) requiring only the warning statement. FDA also generally discussed the agency's reasoning for selecting the proposed regulation over other alternatives. However, FDA's options primarily focused on alternative levels of stringency and informational measures—not on other basic types of regulatory alternatives suggested in the guidance. Also, while FDA included some contextual information in the proposed rule, it did not provide a complete picture of the baseline risks that may be associated with supplements containing ephedrine alkaloids.
- For the actual analysis of potential benefits and costs—the third element—FDA generally adhered to the principles and specific recommendations in OIRA's guidance. For example, FDA discussed the distributional effects of the proposed rule and alternatives in terms of lost sales to the dietary supplement industry. FDA also identified nonmonetized costs associated with the proposed rule. However, FDA did not provide monetized or quantified benefit or cost estimates for all of its regulatory

[33]To conduct a sensitivity analysis, the analyst calculates the costs and benefits of a proposed action using different assumptions.

alternatives, and the agency's discussion of those alternatives' benefits and costs were compared to the proposed rule—not the baseline condition of no regulation as recommended by the guidance.

The OIRA guidance also stresses the importance of full disclosure and transparency in agencies' cost-benefit analyses. We assessed the transparency of FDA's cost-benefit analysis of the proposed rule using three criteria suggested by the guidance:

- first, whether it identified the data, models, inferences, and assumptions used to calculate the estimates of benefits and costs;
- second, whether it disclosed the reasons why those data, models, inferences, and assumptions were selected; and
- third, whether it assessed the effects of plausible alternative assumptions and choices on the results of the analysis—what is often referred to as a "sensitivity analysis."

Overall, we concluded that FDA's analysis was only partially transparent. Using the first criterion, FDA's analysis was very transparent. The agency provided a clear and lengthy description of the data, assumptions, and methodology that it used to calculate the benefits and costs of the proposed rule. Against the second criterion, FDA's analysis was only partially transparent. For most elements of the analysis, FDA identified the underlying data sources used and the rationale for the assumptions and conclusions reached by FDA's analysts and experts. However, FDA did not fully disclose the underpinnings of all of its assumptions and choices. For example, FDA said that between 27 percent and 90 percent of adverse event reports were "probably" related to the consumption of dietary supplements suspected of containing ephedrine alkaloids and that it assumed the value was 80 percent, but it did not indicate why it made this point-estimate assumption. In response to our questions, FDA officials acknowledged that their analysis of impacts was not as transparent as it should have been in explaining how the agency arrived at some of the assumptions regarding its treatment of uncertainty in the underlying data.

Against the third criterion, FDA's cost-benefit analysis was also only somewhat transparent. For example, FDA estimated that the benefits of the proposed rule would be between $240 million and $670 million per year. That estimate was driven by three factors: (1) FDA's estimate of the actual number of adverse events each year (1,110), (2) FDA's estimate of the degree to which the proposed rule would reduce these events (35 percent to 100 percent across all types of proposed actions), and (3) the values FDA

assigned to the estimated risk reduction per case (for example, $5 million per death avoided).[34] Changes in any of these values could have dramatically changed FDA's estimates of the proposed rule's benefits. For example, FDA's estimate of 1,110 adverse events each year was based on an average of 174 adverse events reported per year and three assumptions: (1) that 80 percent of the adverse event reports involved consumption of dietary supplements suspected of containing ephedrine alkaloids, (2) that 80 percent of the supplements actually contained ephedrine alkaloids, and (3) that only 10 percent of all adverse events related to supplements containing ephedrine alkaloids were reported. Using these point estimates (instead of ranges) does not reflect the uncertainty FDA indicated was possible regarding these values and, therefore, the uncertainty associated with the agency's final benefit estimates.

Had FDA used its own initial estimates of the possible ranges (instead of the 80-percent point estimates) for the first two assumptions (27 to 90 percent for the first assumption and 25 to 90 percent for the second assumption), its estimate of the number of adverse events each year would have been 117 to 1,409 instead of a single estimate of 1,110. (See table 2.) If FDA's projected effects for the proposed actions were applied to this range, the expected reduction in annual adverse events would be between 41 and 1,409 cases per year (not the 390 to 1,110 in the published analysis). This ultimately results in a range of potential benefits of roughly $25 million to $850 million per year—a much wider range of possible benefits than the $240 million to $670 million per year estimates that FDA included in the proposed rule.

[34]In its proposed rule, FDA did not report or round its estimated values consistently, so slightly different numbers for the same element appear within the proposed rule. For this report, we are using the values reported in table 6 of FDA's proposed rule, such as 1,110 for the estimated annual number of adverse events.

Table 2: FDA's Estimate of Expected Benefits Is Sensitive to Changes in Key Assumptions

	Assumptions made regarding uncertainty in the actual number of adverse event cases						
A	B	C	D	E (AxBxCxD)	F	G	H (FxG)
Average annual number of reported adverse events	Proportion of cases actually related to dietary supplements	Proportion in which the supplements actually contained ephedrine alkaloids	Multiplier to reflect underreporting of adverse events[a]	Estimated total number of adverse event cases	Estimated reduction in the number of annual cases[b]	Value of estimated risk reduction per case	Total dollar value (in millions) of estimated risk reduction
Scenario 1: FDA's reported results, using a point estimate for total number of adverse events.[c]							
174	0.8	0.8	10	1,110	390-1,110	[d]	$240-670
Scenario 2: Results using the full range of FDA's assumptions regarding uncertainty on number of adverse events.							
174	0.27-0.9	0.25-0.9	10	117-1,409	41-1,409	[d]	25-850
Scenario 3: Results using assumption that 20 percent of cases are reported.							
174	0.8	0.8	5	557	195-557	[d]	118-336
Scenario 4: Results using assumption that 5 percent of cases are reported.							
174	0.8	0.8	20	2,227	779-2,227	[d]	470-1,343

[a]For example, if the assumption is that 10 percent of events are reported, the number of reported cases is multiplied by 10.

[b]The combined effects of all proposed actions are assumed to reduce adverse events by between 35 percent and 100 percent.

[c]FDA's table in the proposed rule on the estimation of benefits displayed rounded numbers. The actual calculated values may vary from the published figures used here. For example, if the figure for estimated total annual adverse events were not rounded, it would equal about 1,114 rather than 1,110.

[d]The value of risk reduction varies by the type of event avoided, such as $5 million per death avoided and $837,000 for each serious cardiovascular system event avoided. FDA converted the individual values and estimated totals into 1996 dollars. Calculations for scenarios 2, 3, and 4 assume the same proportions of types of adverse events as FDA used for its estimate.

Source: Scenario 1 data are taken from table 6 of FDA's proposed rule. Data for other scenarios were GAO calculations using information in FDA's proposal.

Table 2 also shows that changes in the third assumption yield similarly dramatic changes in the estimated benefits. FDA indicated in its proposed rule that reporting rates might be higher than 10 percent if, for example, the potential health risks were widely publicized, or lower than 10 percent if consumers and physicians assumed that dietary supplements are incapable of producing adverse events. If, keeping all other factors constant, FDA had assumed that 20 percent of serious adverse events were reported, FDA's benefits estimate would have been reduced by about half.

Conversely, if FDA had assumed that only 5 percent of events were being reported, the benefits estimate would have doubled.

FDA Met RFA Requirements, Although Questions Remain Concerning Impacts on Industry

RFA requires agencies to consider the effects of their rules on small entities and to take certain actions during the rulemaking process. For example, before publishing a proposed rule for which a notice of proposed rulemaking is required, sections 603 and 605(b) of RFA require a federal agency to prepare and make available for public comment an initial regulatory flexibility analysis that describes the anticipated effects of the proposed rules on small entities, unless the head of the agency certifies that the rule will not have a "significant economic impact on a substantial number of small entities." (See app. V for a more detailed discussion of RFA requirements and our analysis of the actions FDA took to comply with RFA.)

FDA determined that its proposed rule on ephedrine alkaloids would have a significant economic impact on a substantial number of small entities and prepared an initial regulatory flexibility analysis to identify those impacts. FDA's proposed rule addressed the basic elements that RFA requires agencies to include in an initial regulatory flexibility analysis. For example, the rule describes the reasons the agency was considering the action, states the purpose and legal basis of the rule, describes and provides an estimate of the number of small entities to which FDA believed the rule would apply, and describes the compliance requirements. In addition to describing direct compliance costs of between $3 million and $80 million, FDA said that the proposed rule could have significant distributive effects in the form of reduced sales of as much as $230 million a year. FDA explicitly stated that costs and sales reductions of this magnitude might threaten the viability of many firms. FDA also discussed significant regulatory alternatives in the rule's regulatory flexibility analysis section, noting that most of the regulatory alternatives discussed in the cost-benefit analysis section would reduce the impact of the rule on small businesses.

When a rule is promulgated that will have a significant economic impact on a substantial number of small entities, section 609(a) of RFA further requires agencies to ensure that small entities have been given an opportunity to participate in the rulemaking process through the "reasonable use" of outreach efforts. Our review of the regulatory docket for this rulemaking, as well as information obtained during interviews with dietary supplement industry representatives, indicated that FDA provided

opportunities for small business participation during this rulemaking process. For example, in addition to the proposed rule itself, FDA published public notices; held public meetings, during which industry representatives participated and provided testimony; and collected written comments on the issue. Representatives of industry trade associations also told us that FDA had placed notices about the proposed rule in trade literature.

However, SBA's Office of Advocacy criticized the quality of FDA's regulatory flexibility analysis. Along with generally criticizing FDA's scientific analysis for the proposed rule, the office contended that FDA did not consider the large numbers of independent distributors of dietary supplements in its analysis and, as a result, underestimated the number of affected small businesses and the impacts of the proposed actions. In response to SBA's criticism, FDA officials told us that the agency did not need to consider the impact of its proposed rule on distributors of ephedrine alkaloids. FDA officials cited several court decisions that support the proposition that, under RFA, an agency is under no obligation to conduct a small entity impact analysis of effects on entities that the agency does not regulate—that is, distributors.[35]

None of the major parties—FDA, SBA's Office of Advocacy, or industry associations—have information on the actual number of entities involved in the market for dietary supplements containing ephedrine alkaloids. All three parties acknowledge this as a limitation in attempts to analyze the effects of the proposed rule. According to FDA, it has no authority to require companies in the dietary supplement industry either to register with or contact the agency unless they are seeking approval to make a claim in product labeling. However, the industry representatives we met with confirmed that manufacturing and labeling of these products are generally limited to a relatively small number of manufacturing firms. Such firms would bear almost all of the direct expenditures required for compliance with the proposed rule. SBA's Office of Advocacy recommended that FDA develop an outreach strategy to obtain more reliable industry data, and FDA officials said that they have contracted for a marketing study of the dietary supplement industry that should provide better information for future FDA analyses.

[35]For example, United Distribution Cos. v. FERC, 88 F.3d 1105, 1170 (D.C. Cir. 1996).

Proposed Rule Does Not Appear to Trigger UMRA Requirements

UMRA generally requires covered agencies to prepare specific types of analyses for certain rules that include a federal mandate and that may result in the expenditure in any 1 year of $100 million or more by the private sector.[36] FDA did not explicitly address UMRA in its proposed rule on ephedrine alkaloids because its economic analysis indicated that direct expenditures imposed on the private sector would not rise to the level requiring additional analysis under UMRA. FDA estimated that the total compliance costs for the proposed action would be between $3 million and $80 million, with, at most, $70 million of those costs in the first year of implementation. Although FDA also estimated that the rule might result in lost sales for the dietary supplement industry of as much as $230 million per year, lost sales cannot be considered direct expenditures by the private sector and, therefore, cannot be used to trigger UMRA's analytical requirements. (See app. VI for a more detailed discussion of UMRA requirements and our analysis of FDA's compliance.)

However, SBA's Office of Advocacy contended that FDA overlooked the UMRA requirements and commented that if the agency had properly estimated the number of affected businesses and the costs that would be imposed on those entities, "it would have been apparent that the economic impact of the instant rule would impose in excess of $100 million in costs to the industry," triggering UMRA requirements. However, the Office of Advocacy does not have data on the number of entities involved in the market for dietary supplements containing ephedrine alkaloids that it believes should have been included in FDA's analysis. Therefore, the Office of Advocacy could not demonstrate that FDA had underestimated the number of manufacturers that would be affected by the relabeling and reformulation requirements in the rule or that FDA's cost estimates for those manufacturers were in error. Furthermore, even if the expenditures associated with the proposed rule had triggered UMRA's analytical requirements, FDA appears to have satisfied most, if not all, of those requirements. For example, FDA quantitatively and qualitatively assessed the anticipated costs and benefits of the rule. FDA also identified and considered a number of regulatory alternatives, indicating that the other alternatives would not be as effective as the proposed rule.

Conclusions

FDA was justified in determining that the number of AERs relating to dietary supplements containing ephedrine alkaloids warranted their attention and consideration of steps to address safety concerns. The available scientific information suggests that the use of products containing synthetic

[36]The statute provides for annual adjustments for inflation.

ephedrine alkaloids can result in adverse experiences for some individuals, and over-the-counter products containing ephedrine alkaloids have dosing recommendations. Furthermore, dietary supplement trade associations have suggested specific dosing limits for dietary supplements containing ephedrine alkaloids.

However, while FDA's conclusions regarding the desirability of the proposed actions may be valid, we believe these conclusions are open to question because of limitations and uncertainties associated with the agency's underlying scientific and economic analyses. We have concerns about the strength of the information upon which FDA based specific elements of its proposed rule. There is no scientific information on the specific dosing levels and duration limits proposed. FDA, therefore, relied heavily on its AERs to determine a dosing regimen and to outline benefits that would accrue from the proposed rule. However, the AERs suffer from several problems that weaken the conclusions drawn by FDA for their specific dosing regimen; the number of AERs used to support the dosing regimen is small, their quality is questionable, and FDA did not establish a causal link between the ingestion of ephedrine alkaloids and the occurrence of particular adverse events. Finally, because FDA did not document which AERs it identified as involving serious adverse events, it is impossible to verify FDA's calculation of the number of these events and the accuracy of the benefits that FDA estimated would occur as a result of the proposed rule.

FDA's analysis contained the basic elements expected in a federal agency's cost-benefit analysis, and the proposed rule complied with rulemaking requirements under RFA. The proposed rule does not appear to trigger the UMRA analytical requirements. However, FDA's cost-benefit analysis was not always transparent regarding why certain key assumptions were made, the degree of uncertainty involved in those assumptions, or the effect that alternative assumptions would have had on the agency's estimates of the costs and benefits of the proposed action.

Recommendations

Given the uncertainties in the information upon which FDA based its proposed rule, we recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to obtain additional information to support conclusions regarding the specific requirements in the proposed rule for dietary supplements containing ephedrine alkaloids before proceeding to final rulemaking. Specifically, FDA needs to provide stronger evidence on the relationship between the intake of dietary

supplements containing ephedrine alkaloids and the occurrence of adverse reactions that support the proposed dosing levels and duration of use limits.

We also recommend that the Secretary direct the Commissioner to improve the transparency of FDA's cost-benefit analysis in its final rulemaking. Specifically, FDA should more fully explain the bases of its cost-benefit assumptions, the degree of uncertainty associated with those assumptions, and the implications of plausible alternative assumptions to the proposed action and other regulatory alternatives.

Agency and Other Reviewer Comments

We sent a draft of this report to the Commissioner of FDA, the Administrator of SBA, and the Director of OMB. FDA and SBA's Office of Advocacy provided written comments, which are reprinted in appendixes VII and VIII; OMB did not have comments on the report.

In its comments, FDA concurred with our recommendation that it obtain additional information to support its conclusions on specific requirements relating to dietary supplements containing ephedrine alkaloids before proceeding to final rulemaking. FDA also concurred with our recommendation to improve the transparency of the agency's cost-benefit analysis, noting that it intends to take appropriate steps to correct the deficiencies of the analysis prior to publication of a final rule. However, FDA was concerned that our report (1) did not sufficiently highlight the agency's justification in examining safety concerns related to dietary supplements containing ephedrine alkaloids, (2) implied that FDA relied principally on AERs to develop the proposed rule, (3) overemphasized the agency's failure to conduct a causal analysis linking dietary supplements containing ephedrine alkaloids to the AERs, and (4) was not clear on whether it was appropriate to use AERs in rulemaking.

Throughout our report, we express the clear view that given the number and type of AERs, it was reasonable for FDA to investigate the safety of the supplements. We also acknowledge that FDA's actions were based on information from scientific literature as well as AERs. However, although clinical trials suggest that adverse events could occur in some individuals using ephedrine alkaloids at levels approaching 20 mg per serving, they did not provide information relating to adverse events below the 20 mg level. Therefore, to conclude that an 8 mg per serving level would be appropriate, FDA turned to results of tests it performed on a small number of products implicated in 13 AERs. In other words, information from these

AERS was the sole source of support for the specific dosing level of 8 mg per serving that FDA proposed. Finally, we continue to hold the view that without a causal link between the AERS and the ingestion of products containing ephedrine alkaloids, the exclusive use of AERS to support a specific dosing regimen is questionable. FDA also asked that we clarify that using AERS to develop a proposed rule of this type is neither inappropriate nor unscientific. For this report, we examined whether the use of AERS in the proposed rule on dietary supplements containing ephedrine alkaloids was consistent with the use of AERS in prior rulemaking; however, we did not take a position on the appropriateness of the general use of AERS in rulemaking.

SBA's Office of Advocacy stated that our recommendations are reasonable and would result in a more rational—and possibly less burdensome—regulation. However, the officials questioned how we could conclude that FDA had complied with RFA while at the same time suggesting that the agency had prepared an "inadequate analysis" by using unreliable data and not clearly demonstrating that the benefits of the proposed rule exceed the cost. Although our report raises concerns about several aspects of FDA's analysis, we did not conclude that FDA prepared an inadequate analysis. Rather, we concluded that FDA's proposed rule contained the primary elements required under E.O. 12866 for a cost-benefit analysis and under RFA for an initial regulatory flexibility analysis. Furthermore, RFA contains no standards or criteria that define an "adequate" regulatory flexibility analysis. As noted in SBA's comments, section 607 of RFA notes that agencies may provide "general descriptive statements" to comply with the act's analytical requirements if quantification is not practicable or reliable. Determining whether a regulatory flexibility analysis was in compliance with RFA would require analysis and judgments concerning the totality of the circumstances relating to the specific regulation in question. We have no basis and are not in a position to make such a determination regarding the quality of FDA's analysis, nor does our report do so.

SBA's Office of Advocacy also expressed its concern that FDA's analysis did not identify the indirect effects of the rule on distributors. Office of Advocacy officials said that, although certain court decisions stemming from Mid-Tex Electric Cooperative, Inc. v. FERC[37] indicated that agencies need not prepare regulatory flexibility analyses if the effects of a rule on an industry are indirect, they disagreed with those interpretations and contended that agencies should be required to conduct analyses of indirect effects. They also stated that the Office of Advocacy was unaware

[37]773 F.2d 327 (D.C. Cir. 1985).

of any comparable case law with respect to direct and indirect effects as they apply to E.O. 12866, so they said FDA should have prepared an analysis of the rule's effects on distributors. We disagree with these comments for three reasons. First, as the Office of Advocacy officials acknowledged, prior case law indicates that agencies need not take the indirect effects of their rules into account when conducting a regulatory flexibility analysis. That interpretation was recently reaffirmed in a May 14, 1999, decision by the U.S. Court of Appeals for the District of Columbia Circuit.[38] Second, the absence of case law comparable to Mid-Tex with respect to direct and indirect effects as they apply to E.O. 12866 says nothing about FDA's analytical obligations under the order. Third, our review shows that FDA did address the potential indirect effects of the rule through its estimates of total lost sales for the dietary supplement industry. FDA also explicitly acknowledged in the proposed rule that such lost sales are "obviously very significant to the affected parties" and might threaten the viability of many firms in this industry.

We also obtained comments on a draft of this report from a professor of pharmacology with expertise on dietary supplements. He agreed that while there is adequate reason for FDA to be concerned about the safety of products containing ephedrine alkaloids, he believed that there are too few AERs of substantive quality to allow for the setting of a maximum safe dose. He also concurred with our conclusions and recommendations.

FDA provided technical comments, which we incorporated as appropriate.

[38]American Trucking Associations, Inc., et al, v. United States Environmental Protection Agency, No. 97-1440 U.S. App. LEXIS 9064 (D.C. Cir. May 14, 1999).

As agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of this letter. At that time, we will send copies to the Honorable Donna E. Shalala, Secretary of Health and Human Services; the Honorable Jane E. Henney, Commissioner of FDA; the Honorable Aida Alvarez, Administrator of SBA; the Honorable Jacob J. Lew, Director of OMB; and others who are interested. We will also provide copies to others upon request. GAO contacts and major contributors to this report are listed in appendix IX.

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Director of Health Financing
and Public Health Issues

L. Nye Stevens
Director of Federal Management
and Workforce Issues

Contents

Abbreviations

AEMS	adverse event monitoring system
AER	adverse event report
CDC	Centers for Disease Control and Prevention
CFSAN	Center for Food Safety and Applied Nutrition
CPSC	Consumer Product Safety Commission
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GRAS	generally recognized as safe
OIRA	Office of Information and Regulatory Affairs
OMB	Office of Management and Budget
OSN	Office of Special Nutritionals
RFA	Regulatory Flexibility Act
SBA	Small Business Administration
UMRA	Unfunded Mandates Reform Act

Scope and Methodology

To determine whether the reported cardiovascular and nervous system effects outlined in the proposed rule were relevant for dietary supplements containing ephedrine alkaloids and whether there was evidence that these ingredients could cause adverse experiences in some individuals, we examined the scientific literature for case reports of adverse events from ingestion of products containing ephedrine alkaloids and reviewed findings from clinical trials using ephedrine alkaloids to treat obesity. To determine whether the Food and Drug Administration (FDA) had any internal guidance on the use of adverse events reports (AER) in rulemaking and whether these reports had been used in prior rulemaking, we sought information from the agency. We examined five prior cases of rulemaking that FDA provided in which the Center for Food Safety and Applied Nutrition (CFSAN) had used AERs as part of the basis for conclusions that were drawn in a proposed rule to ascertain how the agency had previously used AERs in rulemaking.

In examining the basis for FDA's rule, we evaluated information contained in a sample of AERs and FDA's reliance on them to support a dosing regimen and to estimate benefits from the proposed rule. To identify criteria for the quality of the AERs, we obtained information on the use of passive surveillance systems, including their methodological strengths and weaknesses. We also examined the scientific literature for studies on adverse event reporting and outcomes from such reporting systems. We performed a content analysis of a random sample of 92 out of 864 AERs filed prior to the proposed rule to determine what information was available in the AERs, such as dose, frequency of ingestion, duration of use, type of product, the adverse effect reported, and whether a medical record was included in the report.

We examined the list of 13 AERs used by FDA to set the dosing regimen outlined in the proposed rule. We compared the analytical results of tests performed on the products implicated in these AERs to determine the dosing level ingested by the patient describing the adverse event. We examined the results of these analytical tests to determine the variability in the amount of ephedrine alkaloids that could be found in individual bottles and, thus, the possible range in the amount of ephedrine alkaloids ingested by a complainant. We sought documentation from FDA officials on the AERs that were classed as serious, the numbers and types of each category of serious event, and how those cases had been identified.

We reviewed the extent to which FDA's cost-benefit analysis for the proposed rule contained the elements expected of a federal agency

analysis. To identify criteria for this objective, we reviewed the cost-benefit requirements in E.O. 12866, "Regulatory Planning and Review," and a guidance document issued by the Administrator of the Office of Information and Regulatory Affairs (OIRA) entitled "Economic Analysis of Federal Regulations Under Executive Order 12866." OIRA's guidance was intended to describe "best practices" for agencies in preparing cost-benefit analyses of regulatory actions under the executive order. Using these best practices, we reviewed FDA's cost-benefit analysis in the "analysis of impacts" section of the agency's June 1997 proposed rule. To obtain additional information, we interviewed FDA officials involved in the development of the cost-benefit analysis and the proposed rule. We also reviewed supporting documents referenced in the proposed rule or included in the electronic docket for this rulemaking. As part of that task, we examined each comment related to this rulemaking in the electronic docket to identify substantive remarks on elements of FDA's analysis. We also interviewed officials at OIRA, the Small Business Administration (SBA), and trade associations representing the dietary supplement industry to obtain their views on FDA's cost-benefit analysis.

We used a similar approach to describe FDA's actions to comply with the requirements of the Regulatory Flexibility Act (RFA) and the Unfunded Mandates Reform Act (UMRA). We identified criteria by reviewing the specific requirements in the statutes and then examined the relevant sections of FDA's proposed rule to compare the agency's actions with those requirements. As with the previous task, we supplemented our review of the proposed rule by interviewing officials at FDA, SBA, and industry trade associations. We also reviewed public comments submitted on the proposed rule, including comments submitted by SBA's Office of Advocacy on FDA's compliance with RFA and UMRA.

In our evaluation of FDA's cost-benefit analysis and initial regulatory flexibility analysis, we relied primarily on the information FDA presented in the proposed rule or included in the regulatory docket. We did not perform an independent assessment of the accuracy and reliability of FDA's underlying data and estimates. We also did not examine issues relating to restrictions outlined in the proposed rule relating to ephedrine alkaloids and their use with other stimulants and labeling restrictions.

Adverse Event Reporting

The clinical research and review staff in CFSAN's Office of Special Nutritionals (OSN) is responsible for tracking and reviewing AERs on special nutritional products.[39] Special nutritional products include dietary supplements, infant formulas, medical foods, and foods for special dietary use. The adverse event monitoring system (AEMS) used by OSN is a voluntary surveillance system established to collect information on AERs associated with the use of special nutritional products. Only AERs associated with an illness or injury are included in AEMS; reports of product quality or consumer dissatisfaction are not included. AERs may enter this system through a variety of mechanisms, including FDA's drug quality reporting system, FDA's Medical Products Reporting Program (Medwatch), the United States Pharmacopeia, FDA field offices (through the Office of Regulatory Affairs' consumer complaint system), and from other federal and state public health agencies. Written and electronic correspondence and telephone conversations are other sources of information about adverse events reported with the use of special nutritional products.

When an AER is received, it is reviewed to evaluate the need for further follow-up, including medical record documents, label and labeling, and other types of information necessary for evaluation of the AER. Follow-up is routinely attempted on all AERs of serious events or when the event is deemed to be clinically significant. MedWatch provides guidelines for determining if an adverse event is serious for reporting purposes. Events deemed serious include those that are fatal, life-threatening, or permanently or significantly disabling; require or prolong hospitalization; result in congenital anomalies; or require intervention to prevent permanent impairment or damage.[40] The proposed rule on ephedrine alkaloids includes as serious cardiovascular events abnormal heart rhythms, stroke, heart attack, and cardiomyopathy. Serious nervous system events that were listed in the proposed rule included seizures, psychosis, mania, severe depression, vestibular (inner ear) disturbances, and loss of consciousness. Other reported adverse effects that FDA deemed clinically serious or potentially serious included elevations of liver function tests or overt hepatitis, myopathies (disease of muscle), disturbances of the genitourinary system, and dermatologic manifestations.

AEMS is considered an invaluable tool for identifying potential serious public health issues that may be associated with the use of a particular

[39]Information in this appendix was obtained from a continuing education article from FDA's Center for Drug Evaluation and Research, "The Clinical Impact of Adverse Event Reporting" (Oct. 1996).

[40]Health professionals can report any adverse event that they judge to be clinically significant.

product or types of products. Although more formal epidemiological studies, prospective trials, and retrospective case-control studies are more rigorous, surveillance can be important as an early alert to potential problems. As such, even isolated reports can be definitive in associating products with an adverse effect if the product and effect are temporally related and there is evidence of dechallenge (signs and symptoms resolve or improve when a consumer stops using a product) and rechallenge (symptoms recur when the consumer resumes using the product).

However, like all voluntary surveillance systems, AEMS has certain weaknesses. These limitations include different interpretations in determining an adverse event, underreporting, biases, estimation of population exposure, and report quality. In regard to differing interpretations, it has been well established that AERs are quite subjective and imprecise.[41] For example, in one study, clinical pharmacologists and treating physicians showed complete agreement less than half the time when determining whether medication, alcohol, or recreational drug use had caused hospitalization.[42] It is also well known that placebos[43] and even no treatment[44] can be associated with adverse events. In addition, there is almost always an underlying background rate for any clinical event in a population, regardless of whether there was exposure to a particular product.

Another major concern of passive surveillance systems is underreporting of adverse events. For example, it was estimated that under a British spontaneous reporting system, only 10 percent of serious events and 2 to 4 percent of nonserious events are reported.[45] Another estimate has shown that FDA may receive, by direct reporting, less than 1 percent of suspected serious adverse drug reactions.[46] Thus, the cases spontaneously reported

[41]J. Kock-Weser and others, "The Ambiguity of Adverse Drug Reactions," European Journal of Clinical Pharmacology, Vol. 11 (1977), pp. 75-78.

[42]F. E. Karch and others, "Adverse Drug Reactions—A Matter of Opinion," Clinical Pharmacology Therapy, Vol. 19 (1976), pp. 489-92.

[43]D. M. Green, "Pre-Existing Conditions, Placebo Reactions, and Side Effects," Annals of Internal Medicine, Vol. 60 (1964), pp. 255-65.

[44]M. M. Reidenberg and D. T. Lowenthal, "Adverse Nondrug Reactions," New England Journal of Medicine, Vol. 279 (1968), pp. 678-79.

[45]M. D. Rawlins, "Pharmacovigilance: Paradise Lost, Regained or Postponed?," The William Withering Lecture, 1994, Vol. 29 (London: J. R. Coll. Physicians, 1995), pp. 41-49.

[46]H. D. Scott and others, "Rhode Island Physicians' Recognition and Reporting of Adverse Drug Reactions," Rhode Island Medical Journal, Vol. 70 (1987), pp. 311-16.

to any surveillance program generally represent only a small portion of the number that have actually occurred.

Biases also limit the usefulness of spontaneous reporting systems. Unlike clinical trial data, which are obtained under strictly controlled conditions, spontaneously reported information is uncontrolled and, therefore, subject to the possible influence of a number of reporting biases that are brought about by the length of time a product has been on the market, the reporting environment, and the quality of the data. Compounding these problems, passive surveillance systems lack a denominator for the data, such as user population or drug exposure patterns. This is helpful to provide the exact number of people exposed to a product and, thus, the risk for the adverse event to occur. As a result, incidence rates cannot be computed. Finally, the ability to analyze information contained in an AER is dependent on the quality of information submitted. Optimally, an AER should include product name, demographic data, a clinical description of the adverse event (including confirmatory and laboratory test results), confounding factors (such as medical products and medical history), temporal information, dose and frequency of use, biopsy or autopsy reports, dechallenge and rechallenge information, and outcome.[47]

Although spontaneous reporting systems have a number of weaknesses, they also have advantages over more controlled systems. First, they maintain ongoing surveillance of products that are marketed and, second, they are relatively inexpensive. In fact, they may be the most cost-effective way to detect rare, serious adverse events not discovered during clinical trials.[48] Their usefulness lies in hypothesis generation, to explore cause and effect relationships concerning an adverse event, and as a warning signal of a potential problem with a product. Useful factors for assessing a causal relationship include a chronology of administration of a product, including beginning and ending of treatment and adverse event onset; dechallenge; rechallenge; laboratory test results; and previously known toxicity of an agent or product.

[47]FDA, Center for Drug Evaluation and Research, "The Clinical Impact of Adverse Event Reporting" (Oct. 1996), pp. 5-6.

[48]FDA, Center for Drug Evaluation and Research, "The Clinical Impact of Adverse Event Reporting," p. 6.

FDA's Prior Use of AERs in Rulemaking

AERs have been used by FDA in several rulemaking procedures. In response to a request for prior rules that had relied on AERs, FDA provided five cases, including one in which the "generally recognized as safe" (GRAS) status of an agent (sulfites) was revoked. These cases are outlined in table III.1.

Table III.1: Five Prior FDA Rulemaking Cases

Regulation	Substance	Action
51 Fed. Reg. 25021	Sulfiting agent	Revoked GRAS status for use on fruits and vegetables intended to be served or sold raw to consumers.
51 Fed. Reg. 25012	Sulfiting agent	Required food labeling for foods.
49 Fed. Reg. 13679	Protein supplements	Required warning labeling.
62 Fed. Reg. 2218	Supplements and drugs containing iron	Required label warning statements and unit-dose packaging.
44 Fed. Reg. 37212	FD&C[a] yellow no. 5	Required labeling in food and drugs for human use.

[a]Food, Drug, and Cosmetic.

Sulfiting Agents and GRAS Status

FDA's proposed rule to revoke GRAS status for sulfiting agents resulted after the agency received information on the use of sulfur dioxide, sodium sulfite, sodium bisulfate, potassium bisulfate, sodium metabisulfate, and potassium metabisulfate (collectively known as sulfiting agents, or sulfites) on fruits and vegetables intended to be served raw or sold raw to consumers and it concluded that such use was not safe. This rule, similar to the ephedrine alkaloid ruling, used AERs, advisory panels, clinical studies, and case reports to determine whether sulfiting agents should maintain its GRAS status.

FDA had received over 500 consumer complaints, where individuals reportedly suffered from a variety of adverse allergic-type responses, including reports of 13 deaths; the proposed rule indicated that these responses tended to occur in people with asthma.[49] Among the 500 AERs, approximately 40 percent mentioned the occurrence of the event after eating raw fruits and vegetables in restaurants (where sulfiting agents are used), while 15 percent specifically mentioned the occurrence of the event after drinking wine or beer. The proposed rule delineated the clinical outcomes from these adverse reactions, ranging from gastrointestinal

[49]FDA relied on prevalence estimates that indicated there are 10 million individuals with asthma in the United States, with up to 10 percent sulfite-sensitive. See Select Committee on GRAS Substances, "The Reexamination of the GRAS Status of Sulfiting Agents," Life Sciences Research Office, Federation of American Societies for Experimental Biology, prepared under FDA contract 223-83-2020 (Jan. 28, 1985).

problems to anaphylactic shock (hypersensitivity reactions characterized by swelling, erythema, bronchoconstrictions, and hypotension).

A scientific panel also reviewed the AERs submitted to FDA and concluded that the reports indicated an association between adverse responses and the ingestion of meals that included foods containing sulfiting agents. The panel also examined exposure estimates and evidence from clinical experiments during its review on this topic.

While this rule and the ephedrine alkaloid rule are similar—because the AERs used in the rulings simply highlighted the number of complaints and provided a breakdown of the complaints' origins and clinical complications—the proposed rule on sulfiting agents outlined additional information not found in the proposed rule for ephedrine alkaloids. This included information on exposure estimates, prevalence rates within sensitive populations, and clinical experiments involving the exposure of sensitive and nonsensitive populations to sulfiting agents. In addition, dosing regimens were not set for sulfiting agents because the proposed rule revoked their GRAS status.

Sulfiting Agents and Food Labeling

The proposed rule for the labeling of products containing sulfiting agents was designed to clarify the circumstances in which the presence of sulfiting agents must be declared on food labels. FDA noted in this proposed rule that any detectable amount of a sulfiting agent would require that the product be labeled because the agency was unaware of any evidence that established a level below which these substances would not cause a reaction in sensitive individuals. FDA relied on scientific data on human sensitivity to sulfiting agents to establish that certain sensitive individuals—in particular, those with asthma—could react to ingested sulfiting agents. FDA also used estimates of the number of individuals with asthma and clinical studies on those who were sensitive to sulfiting agents to determine the number who might be adversely affected. Last, FDA formed an ad hoc advisory committee on hypersensitivity to sulfiting agents in food to review and evaluate available data on adverse reactions in humans associated with the use of sulfiting agents in food. This rule did not describe, in any appreciable detail, adverse events.

Labeling for Protein Supplements

In December 1997, FDA proposed labeling requirements for protein supplements that were used in weight reduction programs. The purpose of the rule was to alert consumers to the potential health hazards associated

with consuming protein supplements to control weight and to inform consumers that the advice of a physician should be sought before using these products for weight control. The agency proposed these requirements on the basis of evidence that, without proper medical supervision, low-calorie diets consisting primarily of protein may cause serious medical problems, including death. The proposed rule noted that an ad hoc advisory group had been formed to examine several cases of deaths associated with individuals using these protein products as their primary source of nourishment.

A tentative final rule published on December 29, 1978, noted that more than 165 reports of adverse reactions attributed to consumption of protein products by consumers attempting to lose weight had been reported to the FDA. These complaints—described as "very diverse"—included nausea, tachycardia (rapid heart rate or palpitations), breathlessness, and headaches.[50] Review of these reports by FDA revealed no consistent pattern of complaints or reactions, and the tentative final rule concluded that "a cause-and-effect relationship can neither be affirmed nor rejected on the basis of the existing information from these reports." The rule further stated that "There were sufficient details among the reported adverse reactions . . . to warrant concern."

FDA further asserted that imposing a warning on the labeling of these protein products—even with the gaps in their understanding of the basic mechanism of how these protein supplements affected the body—was particularly appropriate because the consequence of indiscriminate use of these products was death. FDA also noted that the protein products were not inherently dangerous and that the label warning was proposed to curb misuse of these products and because the products were being sold directly to consumers who might not be under proper medical supervision.

Data were collected through a telephone survey, conducted by FDA and CDC, to determine the extent of use of protein products. This information was used to establish a death rate by combining this information with data on deaths among liquid protein dieters from the same population group. This information was compared with data from the National Center for Health Statistics on annual death rates due to cardiac abnormalities among a similar population group. FDA concluded that the observed death rate was greater in those who used low-calorie protein diets. FDA also initiated experimental protocols using laboratory rats in order to explore the basic

[50]After a court challenge from the National Nutritional Foods Association, a final rule was published on April 4, 1984.

mechanisms for the cause of death. These studies were designed to assess the correlation of cardiac arrhythmias (irregular heartbeat) and death with various aberrant states of nutrition health and rate of weight loss.

Supplements and Drugs Containing Iron

In October 1994, FDA proposed warning labels and unit-dose packaging requirements[51] for products taken in solid oral form to supplement the dietary intake of iron or to provide iron for therapeutic purposes. The labeling was proposed because of evidence of acute iron poisoning attributable to accidental overdoses of iron-containing products and an upsurge in reported accidental pediatric ingestion of iron-containing products, which, in some cases, resulted in death.[52]

FDA relied on data from the American Association of Poison Control Centers and the U.S. Consumer Product Safety Commission (CPSC) that highlighted increases in reported fatalities from accidental iron poisonings of children. Over 63,000 reports were taken at poison control centers involving ingestion of adult iron-containing products, with over 47,000 of these involving children under 6 years of age. One hundred and fifty-nine cases were classified as major outcomes; that is, they were life threatening or resulted in permanent injury. An additional 1,500 cases were classified as "moderate outcomes"; that is, the patient had symptoms that required some form of treatment. Over 76,000 reports to these centers involved ingestion of pediatric iron-containing products with children under 6 years of age.

Likewise, data from the National Electronic Injury Surveillance System—a probability sample of hospital emergency rooms in the United States used by CPSC to measure the magnitude of injury associated with consumer products—found a significant upward trend in the estimated number of hospital emergency-room-treated iron-ingestion cases involving children under 5 years of age. The proposed rule also outlined data collected by CPSC on case reports of pediatric deaths, including the number of tablets taken, the potency (dosage), and total amount ingested. Additionally, a conference was held by CPSC to examine the reason for the increase in iron poisonings among children.

[51]Unit-dose packaging is designed to prevent the unintended ingestion by children, not to control the recommended dose for adults.

[52]U.S. Consumer Product Safety Commission, "Pediatric Iron Poisonings and Fatalities" (May 1994), p. 3.

The final rule expanded on the information that was used as the basis for warning labels by outlining the results of animal toxicity studies, acute toxicity in humans, comparison of animal toxicity data to human toxicity data, and physiological factors that influence toxicity. Thus, information used by FDA in its proposed and final rules on iron-containing products included data from CPSC, case reports from adverse reactions, and scientific literature.

FD&C Yellow No. 5

In its proposed rule of February 4, 1977, FDA noted that there was accumulating evidence that FD&C yellow no. 5 (tartrazine) caused allergic-type responses, especially in aspirin-intolerant individuals.[53] Thus, FDA was proposing to require a label declaration of FD&C yellow no. 5 when used to color foods and ingested drugs and to prohibit its use in certain drugs for human use. FDA noted in the proposed rule that "the precise incidence of intolerance of FD&C yellow no. 5 in the total population or even in aspirin-intolerant patients is not known." However, FDA did outline a number of case reports and studies highlighting that these effects did occur and that some quantification regarding subpopulations at risk could be identified. Specifically, FDA estimated that approximately 47,000 to 94,000 people would be intolerant to tartrazine. But this proposed rule did not denote how many case reports or adverse drug reactions formed the basis for FDA's actions. Instead, the primary information used in the proposed and final rule related to scientific studies demonstrating individual intolerance to tartrazine.

[53]In the final rule, FDA required a label declaration of FD&C yellow no. 5 when used to color foods and drugs for human use.

FDA's Analysis of Benefits and Costs

E.O. 12866 and related guidance from OIRA state that cost-benefit analyses should contain three basic elements: (1) a statement of the need for the proposed action, (2) an examination of alternative approaches, and (3) an analysis of benefits and costs. Overall, the guidance indicates that an analysis should be "transparent." We concluded that FDA's cost-benefit analysis contained, to some degree, all three of the recommended elements in such analyses. FDA also disclosed the basic methodology, data, and assumptions used in its analysis. However, the cost-benefit analysis was not always transparent regarding why certain key assumptions were made, the degree of uncertainty involved in those assumptions, or the effect that alternative assumptions would have had on the agency's estimates of the costs and benefits of the proposed action.

E.O. 12866 and Related Guidance Set Agency Responsibilities for Analysis of Benefits and Costs

Conceptually, a cost-benefit analysis is a rigorous and data-intensive procedure of weighing the costs and benefits of various alternatives to a proposed action, informing decisionmakers about the potential consequences of each. However, the results of the analysis, by themselves, do not determine whether or how an agency will regulate in response to a perceived problem.

E.O. 12866 requires agencies to conduct cost-benefit analyses for all regulatory actions that are likely to result in a $100 million annual effect on the economy or are otherwise economically significant. The executive order also makes OIRA responsible for reviewing all significant regulatory actions and for providing guidance to agencies on issues covered by the order. On January 11, 1996, the Administrator of OIRA issued guidance describing "best practices" for preparing cost-benefit analyses.[54] The guidance makes clear that it is not a "mechanistic blueprint" and provides for flexibility and the exercise of professional judgment in preparing analyses. However, the guidance does establish one clear expectation of all such analyses:

> Analysis of the risks, benefits, and costs associated with regulation must be guided by the principles of full disclosure and transparency. Data, models, inferences, and assumptions should be identified and evaluated explicitly, together with adequate justifications of choices made, and assessments of the effects of these choices on the analysis. The existence of plausible alternative models or assumptions and their implications should be identified. In the absence of adequate valid data, properly identified assumptions are necessary for conducting an assessment.

[54]The OIRA guidance was developed as a result of a 2-year study by an interagency group that included representatives of all the major regulatory agencies and was co-chaired by a member of the Council of Economic Advisers.

Within this broad framework, the OIRA guidance states that analyses of economically significant rules should contain three basic elements: (1) a statement of the need for the proposed action, (2) an examination of alternative approaches, and (3) an analysis of benefits and costs. Within each of these three elements, the guidance recommends that certain items be considered or analytical approaches be used in preparing an agency's analysis. For example, in relation to the third requirement, the guidance says the analysis should identify and explain the data or studies on which the estimates of benefits and costs are based "with enough detail to permit independent assessment and verification of the results." The guidance also states, "where benefit or cost estimates are heavily dependent on certain assumptions, it is essential to make those assumptions explicit and, where alternative assumptions are plausible, to carry out sensitivity analyses based on the alternative assumptions." The purpose of such disclosure is to allow for a reasoned determination by decisionmakers of the appropriate level of regulatory action.

FDA's Analysis Addressed the Primary Elements Suggested by OIRA Guidance

FDA indicated in the proposed rule that the regulation was economically significant, and FDA officials told us that they used the OIRA guidance in developing the cost-benefit analysis for the rule. We compared FDA's cost-benefit analysis to the elements and practices outlined in that guidance and concluded that FDA's analysis addressed the primary elements suggested by the OIRA guidance. However, certain specific elements appeared to be lacking.

Need for Regulation

The OIRA guidance states that in establishing the need for the proposed action, agencies should discuss (1) whether the problem constitutes a significant market failure that compels government action and (2) if there is a market failure, the appropriateness of alternatives to federal regulation that would resolve the problem adequately or better than the proposed rule. Among the types of market failures that the guidance says agencies can discuss are monopolies and inadequate information available to consumers about product characteristics. The guidance states that alternatives to federal regulation can include subsidies or fees that may be more efficient than rigid mandates or state and local regulation that would be more appropriate.

FDA stated in the proposed rule that the rule was needed because of a significant market failure—specifically, inadequate information. FDA said that despite the presence of warning labels of various types on many of the products, "some consumers may not have sufficient information on the

health risks associated with dietary supplements containing ephedrine alkaloids to make informed choices concerning the consumption of these products." Among other points, FDA said that the level of information currently used by consumers might be less than optimal because of consumer perceptions that products marketed as foods or derived from botanical sources are inherently safe.

However, FDA did not directly address the second major item in the guidance under the need for action section—whether alternatives to federal regulation would resolve the problem adequately or better than the proposed federal regulation. In particular, FDA did not recognize that several states were in the process of regulating these products and did not discuss whether federal regulation was superior to those state regulations (for example, because these products are marketed across state lines).

Examination of Alternative Approaches

The OIRA guidance states that an agency's cost-benefit analysis should demonstrate that the agency has considered the most important alternative approaches to the underlying problem and should provide the agency's reasoning for selecting the proposed regulation over such alternatives. The guidance notes that the number and choice of alternatives to be selected for a detailed cost-benefit analysis is a matter of judgment but says the agency should nevertheless "explore modifications of some or all of a regulation's attributes or provisions to identify appropriate alternatives." The guidance also states that the agency should explore a number of different types of regulatory alternatives, including

- more performance-oriented standards for health, safety, and environmental regulations;
- different requirements for different segments of the regulated population;
- alternative levels of stringency;
- alternative effective dates of compliance;
- alternative methods of ensuring compliance;
- informational measures (for example, mandatory disclosure requirements, such as labeling);
- more market-oriented approaches; and
- consideration of whether the agency should adopt a more stringent standard than already established by statutory requirements.

In the proposed rule, FDA identified seven regulatory "options": (1) take no action (the baseline alternative); (2) take no action, but generate additional information; (3) take the proposed action; (4) take the proposed

action but with a higher potency limit; (5) ban dietary supplements that contain ephedrine alkaloids; (6) take the proposed action, but do not require the warning statement; and (7) require only the warning statement.

In general, FDA's options focused primarily on the OIRA guidance categories of alternative levels of stringency and informational measures. FDA did not appear to explore performance-oriented standards, different requirements for different segments of the regulated population, market-oriented approaches, or alternative effective dates of compliance. However, it is unclear whether these types of alternatives could legitimately be considered for the proposed regulation. For example, it is unclear how FDA could establish market approaches, such as additional fees on the dietary supplement industry, or performance standards for health effects.

In comments on the rule, industry representatives and SBA's Office of Advocacy identified what they viewed as a weakness related to FDA's baseline description of the world absent the proposed regulation. FDA presented information on the number of adverse events believed to be associated with ephedrine alkaloid products and described an increasing trend in reported adverse events. However, industry representatives and SBA said FDA did not provide sufficient information to put these data in a meaningful context. For example, they said there was no information on general probabilities or risks of people suffering the types of adverse events that FDA attributed to ephedrine alkaloid products. They also said that FDA did not provide information to put the aggregate number and growth in reported adverse events in the context of total consumption of dietary supplements that might contain ephedrine alkaloids. SBA's Office of Advocacy and industry trade associations commented that consumption of such supplements might be in the billions of doses. In that context, they contended that adverse events associated with the consumption of dietary supplements containing ephedrine alkaloids may occur at very low rates, perhaps lower than those for some over-the-counter drugs.

On the other hand, FDA did provide some contextual information in the proposed rule on the incidence of adverse events for dietary supplements as a whole. FDA's data indicated that AERs believed to be associated with supplements containing ephedrine alkaloids accounted for approximately 50 to 60 percent of the total number of reports received by FDA when the rulemaking was initiated. FDA officials told us that the number of AERs in their system suspected of involving ephedrine alkaloids "jumped out" compared with the numbers for any other substances, although they have not done any detailed analysis or tally to document numbers for other

substances. Representatives of industry trade associations who we met with acknowledged that the incidence of adverse events for supplements containing ephedrine alkaloids is greater than would be expected for most other dietary supplements. Still, providing only this contextual information in the proposed rule does not appear to provide a balanced or complete picture of the baseline risks that may be associated with supplements containing ephedrine alkaloids.

Analysis of Benefits and Costs

The bulk of OIRA's guidance is devoted to addressing the third element, analysis of benefits and costs. In this section, the guidance first presents general principles on (1) measuring the benefits and costs of each alternative against a baseline condition of the way the world would look absent the proposed regulation, (2) evaluation of alternatives, (3) discounting costs and benefits that may occur at different points in time, (4) treatment of risk and uncertainty, (5) assumptions used in the analysis, (6) international trade effects, (7) nonmonetized benefits and costs, and (8) distributional effects and equity. These general principles are followed in the OIRA document by more detailed guidance on the analysis of benefits and costs. For example, within the benefits section, the guidance states that reductions in illnesses, injuries, and fatalities as a result of government action are best monetized according to a "willingness to pay" approach.[55] The guidance also emphasizes that benefits and costs should be "incremental," representing changes from the baseline condition of no regulation, and that the analysis should identify and explain the data or studies on which the estimates are based "with enough detail to permit independent assessment and verification of the results."

In its analysis of benefits and costs, FDA adhered to a number of the recommendations in the OIRA guidance. For example, the analysis discussed distributional effects of the proposed rule and alternatives in terms of lost sales to the dietary supplement industry. FDA also discussed nonmonetized costs associated with the proposed rule, and it monetized the benefits associated with reductions in various types of adverse events using the willingness-to-pay approach recommended in the guidance. In addition, the analysis presented the monetized costs of the proposed rule against the baseline condition of no regulation. However, FDA did not provide monetized or quantified benefit or cost estimates for all of the other alternatives, and the agency's discussion of those alternatives' benefits and costs were compared to the proposed rule—not the baseline

[55]The principle of "willingness to pay" captures the notion of opportunity cost by providing an aggregate measure of what individuals are willing to forgo to enjoy a particular benefit.

condition of no regulation. For example, in relation to the benefits associated with allowing higher potency levels (option 4) compared to FDA's proposal (option 3), FDA said that the effect would be to "reduce those benefits below those generated under option 3." (FDA officials told us during our review that the agency attempted to reach a balance in conducting the analysis and said the analysts try to quantify the effects of alternatives when such information would be of value to decisionmakers.)

Also, some parts of FDA's analysis of these alternatives were either unclear or illogical. For example, in relation to the option of banning dietary supplements that contain ephedrine alkaloids (option 5), FDA stated that "banning these products would decrease access to these products by consumers." It is not clear why a total ban in the products would not eliminate—not just decrease—access. Similarly, FDA also said "the total reduction in the consumption of dietary supplements that now contain ephedrine would probably be approximately 33 percent under this option." It is not clear why a ban would only reduce consumption by 33 percent. Another unclear element of the analysis concerns discounting. The guidance recommends that dollar estimates should be discounted and reported in same-year dollars. Although FDA noted that it converted dollar figures for its estimates of monetized benefits to 1996 dollars, it did not identify in the proposed rule whether its total cost estimates were also expressed in 1996 dollars.

As a result of its analysis, FDA concluded that the proposed rule would generate benefits of between $240 million and $670 million per year, quantifiable costs of between $3 million and $70 million in the first year, and quantifiable costs of between "a minimal amount" and $500,000 in each subsequent year. FDA justified the selection of the proposed rule over the other regulatory alternatives in terms of the greater net benefits expected of the proposed actions.

Analysis Did Not Fully Explain Some Key Assumptions or Assess Implications of Alternative Assumptions

The OIRA guidance emphasizes the importance of full disclosure and transparency of key data and assumptions in cost-benefit analyses. As noted previously, the guidance says that "data, models, inferences, and assumptions should be identified and evaluated explicitly, together with adequate justifications of choices made, and assessments of the effects of these choices on the analysis." Therefore, we assessed the transparency of FDA's cost-benefit analysis of the proposed rule in terms of three criteria:

- first, whether it identified the data, models, inferences, and assumptions used to calculate the estimates of benefits and costs;
- second, whether it disclosed the reasons why those data, models, inferences, and assumptions were selected; and
- third, whether it assessed the effects of plausible alternative assumptions and choices on the results of the analysis—what is often referred to as a "sensitivity analysis."

Identification of Data and Assumptions

In relation to the first criterion, FDA's analysis was very transparent. The agency provided a clear and lengthy description of the data, assumptions, and methodology that it used to calculate the benefits and costs of the proposed rule. For example, in calculating the annual monetized benefits of the proposed rule, FDA identified for each of six categories of adverse events (for example, deaths, serious cardiovascular system events, serious nervous system events, and abnormal liver functions) (1) the annual number of reported adverse events (based on the average number of AERs received each year), (2) the estimated total number of such events each year, (3) the estimated number of cases that would be reduced by implementation of the proposed rule, (4) the monetized value of each reduced case, and (5) the estimated value of the total risk reduction (the number of reduced cases times the value of each case).

FDA also identified many of the underlying assumptions that it used in developing these elements. For example, in developing its estimate of the total number of annual cases, FDA noted that it assumed that (1) 80 percent of the reported adverse events suspected of involving supplements containing ephedrine alkaloids were actually related to the consumption of dietary supplements, (2) 80 percent of these supplements actually contained ephedrine alkaloids, and (3) only 10 percent of adverse events related to ephedrine alkaloids were actually reported. In similar fashion, FDA disclosed how it calculated the estimated compliance costs of the rule, including the one-time costs associated with relabeling and reformulating the affected supplements.

Explanation of Assumptions

In relation to the second transparency criterion—explaining the reasons for choices made for key assumptions and values—FDA's analysis was only partially transparent. For most elements of the analysis, FDA identified the underlying data sources used and the rationale for the assumptions and conclusions reached by FDA's analysts and experts. The proposed rule included a lengthy discussion about the scientific data and studies FDA and

its advisory committees reviewed in developing the various provisions of the rule. In estimating the effects of these provisions, FDA also identified the underlying data sources and analysis in most cases. For example, in its discussion on potential relabeling costs, FDA described how it used data from a previous FDA rule on nutrition labeling of dietary supplements to derive its estimate of the specific costs for this rule. In describing how it estimated the effect of restrictions on including other stimulants in supplements containing ephedrine alkaloids, FDA discussed the results of a clinical study on combinations of ephedrine and caffeine and the results of its informal review of adverse event reports.

However, FDA did not fully disclose the underpinnings of all of its assumptions and choices. In particular, although FDA identified the values it used to estimate the number and severity of adverse events for its calculation of benefits, its explanation of the underlying data sources, analyses, and basis for the selected values was not complete. In its analysis, FDA identified three main areas of uncertainty in its estimation of the actual number of adverse events believed to be attributable to use of products containing ephedrine alkaloids. These areas were (1) the proportion of reported adverse events that were actually related to consumption of dietary supplements, (2) the proportion of reported adverse events that involved supplements that actually contained ephedrine alkaloids, and (3) the proportion of adverse events that were actually reported. For each of these elements, FDA assumed a particular value that drove up the estimated number of actual adverse events and, as a direct consequence, the estimated benefits of the proposed rule. However, FDA did not always disclose why it selected those values or why it selected a single value instead of a range of values that would have more clearly represented the degree of uncertainty that FDA believed was present.

In relation to the first area of uncertainty, FDA estimated that between 27 and 90 percent of the reported adverse events were "probably" related to the consumption of dietary supplements suspected of containing ephedrine alkaloids. However, FDA did not clearly disclose the basis for estimating this range. Within this range, FDA assumed that 80 percent of the reported adverse events were actually related to the consumption of dietary supplements. FDA did not disclose how it arrived at the choice of 80 percent as the "most likely" value. Furthermore, in calculating the "range" of estimated benefits for the proposed rule, FDA used only this point estimate, not the entire 27 to 90 percent range, or a more narrowly focused range of values in calculating the expected number of cases. Use

of a range of values for this element would have more clearly represented the uncertainty regarding the number of AERs actually related to the consumption of dietary supplements.[56]

The second source of uncertainty that FDA identified was the extent to which all AERs involved products that actually contained ephedrine alkaloids. FDA estimated that the proportion of reported adverse events associated with dietary supplements containing ephedrine alkaloids was "probably" between 25 and 90 percent based on (1) the labeling of the products involved, (2) FDA's own market study and laboratory analysis of 125 marketed products, and (3) the similarity of the reported adverse events to the known effects of ephedrine alkaloids. Within this range, FDA assumed that 80 percent of the reported adverse events associated with the consumption of dietary supplements involved supplements that contained ephedrine. FDA did not disclose why it selected 80 percent as the "most likely" value. Finally, as was the case in the first area of uncertainty, FDA used only this 80 percent point estimate, not the full range or an attenuated range of values, in calculating the expected number of annual cases.

FDA's third identified source of uncertainty was the likelihood that all adverse events related to ephedrine alkaloids were probably not being reported. FDA noted in the analysis that typical reporting rates for passive reporting systems on adverse events associated with pharmaceutical drugs are "generally assumed to be on the order of 10 percent." However, FDA noted that reporting rates might be higher than usual if, for example, the potential health risks are widely publicized, or lower than normal if consumers and physicians assume that dietary supplements are incapable of producing adverse events. FDA said that "to incorporate this uncertainty," it assumed that the reporting rate for the adverse events related to ephedrine alkaloids was 10 percent. It was not clear how a single point estimate of 10 percent would "incorporate" the uncertainty that FDA identified for this value.

In response to our questions about these uncertainties, FDA officials acknowledged that their analysis of impacts was not as transparent as it should have been in explaining how the agency arrived at some of the assumptions. The Director of FDA's Market Studies Division, which prepared the cost-benefit analysis, explained that the estimated

[56]FDA was somewhat inconsistent in its use of point estimates versus ranges. FDA used its full estimated range of adverse events in projecting the results for other regulatory options, such as banning supplements with ephedrine alkaloids. FDA officials said that they chose to use the full ranges in discussing other options because of the regulatory actions in those options.

proportions and the selected values represented the best professional judgment of FDA's analysts and experts. He noted that the upper-bound estimate of 90 percent for the first two areas of uncertainty represented what the analysts believed was a reasonable choice for the "absolute most it could be." He said that the lower-bound estimate of 27 percent for the first category was derived from the cases in the AERS in which people who stopped using products suspected of containing ephedrine alkaloids no longer experienced the effects associated with the adverse event. Similarly, FDA's figure of 25 percent as the most reasonable low-end estimate for the second category was based on FDA's review of samples of products mentioned in the AERS. He said that the choice of 80 percent as the most likely value for both of these categories was a determination made by FDA's scientific experts, given all the available data and scientific evidence they had reviewed, not just the AERS.

The director and other FDA officials indicated that FDA had much more confidence in the estimate that only 10 percent of actual adverse events were reported. They said that, compared to the other two sources of uncertainty, FDA knows more about AEMS and is also familiar with studies of other passive reporting systems used by FDA and other federal agencies. The officials noted that, for other systems, they have done reviews for specific sites (for example, going to hospitals to check records and do testing) and found that reporting rates were about 10 percent. The director said that FDA did not provide a range for this category in the proposed rule because FDA was confident in the point estimate and because it did not have any way—other than through an "artificial exercise"—to come up with a range of possible values.

Implications of Alternative Assumptions

FDA's cost-benefit analysis was also only somewhat transparent with regard to the third of our transparency criteria—assessment of the effects of plausible alternative assumptions and choices on the results of the analysis. The degree of transparency in this area and the sensitivity of FDA's results to alternative assumptions are most clearly illustrated in the agency's estimate of expected benefits.

FDA estimated that the benefits of the proposed rule would be between $240 million and $670 million per year. That estimate was driven by three factors: (1) FDA's estimate of the number of adverse events each year (1,110), (2) FDA's estimate of the degree to which the proposed rule would reduce these events (35 percent to 100 percent across all types of proposed actions), and (3) the values FDA assigned to the estimated risk

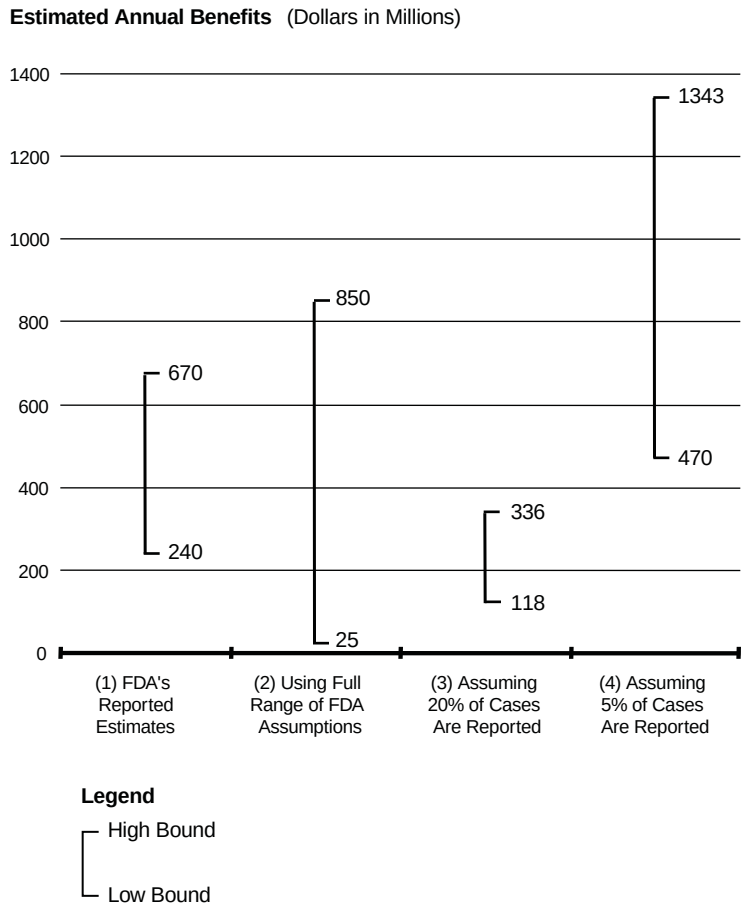
reduction per case (for example, $5 million per death avoided).[57] Changes in any of these values could have dramatically changed FDA's estimates of the proposed rule's benefits. By using the 35 to 100 percent range for the second factor (and even wider ranges for some of the individual actions), FDA illustrated the sensitivity of the analysis to changes in particular values. This second factor was the only component in FDA's calculations that generated a "range" in the estimated reduction in annual adverse events (390 to 1,110) and, in turn, the size of the expected benefits ($240 million to $670 million).[58]

On the other hand, FDA's estimate of the 1,110 estimated adverse events each year (factor 1) was based on an average of 174 adverse events reported per year and the three assumptions about adverse events—that 80 percent of the AERs involved dietary supplements, that 80 percent of the supplements contained ephedrine alkaloids, and that only 10 percent of all adverse events related to supplements containing ephedrine alkaloids were reported. FDA's use of these point estimates (instead of ranges) does not reflect the sensitivity of the final benefit estimates to these assumptions. As illustrated in figure IV.1, the results of FDA's estimation of expected benefits are, therefore, very sensitive to changes in the underlying assumptions. If FDA had used other plausible assumptions, based on the information it presented in the proposed rule, the ranges of expected benefits would have varied noticeably from the values FDA presented in its proposal.

[57]In its proposed rule, FDA did not report or round its estimated values consistently, so slightly different numbers for the same element appear within the proposed rule. For this report, we are using the values reported in table 6 of FDA's proposed rule, such as 1,110 for the estimated annual number of adverse events.

[58]Similarly, FDA's $3 million to $80 million range in the estimated cost of the proposed rule also reflects the sensitivity of the agency's assumptions.

Figure IV.1: Estimation of Benefits Is Sensitive to Changes in Underlying Assumptions



Note: The data for scenario 1 are from FDA's reported estimates in table 6 of the proposed rule. Scenario 2 was calculated using the full range of assumptions FDA presented in the narrative of its proposed rule regarding key assumptions about the number of adverse events each year. Scenarios 3 and 4 were calculated changing only FDA's selected assumption regarding the reporting rate for adverse events. All other assumptions were held constant.

Source: Scenario 1 data are taken from table 6 of FDA's proposed rule. Data for other scenarios were GAO calculations using information in FDA's proposal.

Given the uncertainty surrounding most of the key data and assumptions used in FDA's analysis, similar types of sensitivity analyses could be done using alternative choices for other elements in the analysis, such as the following:

- FDA used published estimates of the value that consumers place on reducing certain types of risk to estimate the monetary value benefits associated with the proposed rule. However, other published estimates for these values could also have been used. For example, FDA assumed in its analysis that the value of avoiding a death was $5 million. We have reported that the Environmental Protection Agency's (EPA) assumptions regarding the value of avoiding a death have ranged from $1.6 million to $12 million.[59]
- FDA's estimates of the benefits of the rule were also a function of the distribution of the types of adverse events (for example, deaths, cardiovascular system events, and neurological system events) reported through the underlying AERs. Given that there is sufficient uncertainty regarding the reports that different distributions of the numbers of events are plausible, FDA's analysis could have reflected these alternative distributions and the effect they would have had on the benefit estimates.
- FDA's estimates of the costs of the proposed rule were based, in part, on assumptions regarding the number of dietary supplement products sold and the number of businesses involved in the dietary supplement market. As discussed in appendix V, "Regulatory Flexibility Act Requirements," there is considerable uncertainty about the actual number of businesses and products involved in the market for dietary supplements containing ephedrine alkaloids.

As FDA officials noted in our meetings with them, there are limits to the amount of effort that can be expended on an analysis, and they attempt to reach a balance in conducting a reasonable effort. They pointed out that the proposed rule was long and that they had struggled to keep the length of the narrative under control. However, the OIRA guidance recommends that agencies carry out sensitivity analyses over the full range of plausible values of key parameters, particularly when there are several easily identifiable critical assumptions in the analysis and information is inadequate to carry out a more formal probabilistic simulation for assessment of risks. In this respect, FDA's focus on presenting the agency's "best estimate" does not seem to fully reflect the uncertainty in the underlying data and analysis or the expectations set by the OIRA guidance. In explaining why FDA did not do a sensitivity analysis for this proposed rule, the Director of the Market Studies Division said that, at this point in time, risk assessors are ahead of cost-benefit analysts in doing sensitivity analyses. He did note that, while FDA did not do a sensitivity analysis for

[59]Regulatory Reform: Agencies Could Improve Development, Documentation, and Clarity of Regulatory Economic Analyses (GAO/RCED-98-142, May 26, 1998), and Air Pollution: Information Contained in EPA's Regulatory Impact Analyses Can Be Made Clearer (GAO/RCED-97-38, Apr. 14, 1997).

this particular proposed rule, it would probably do more sensitivity analyses in the near future.

Regulatory Flexibility Act Requirements

The Regulatory Flexibility Act requires agencies to consider the effects of their rules on small entities. FDA determined that its proposed rule on dietary supplements containing ephedrine alkaloids would have a significant economic impact on a substantial number of small entities. Therefore, FDA prepared an initial regulatory flexibility analysis to identify the potential impacts of the proposed rule and alternative actions on affected small businesses. Also, as required by RFA, FDA provided opportunities for small business participation in the rulemaking process. However, while FDA addressed the basic requirements of the act, SBA's Office of Advocacy criticized the quality of FDA's regulatory flexibility analysis. For example, the office contended that FDA underestimated the number of affected small businesses and the impacts of the proposed actions by not considering the large numbers of independent distributors of dietary supplements in its analysis.

Regulatory Flexibility Act Requires Agencies to Consider Impact of Regulation on Small Businesses

During the past 20 years, the Congress has enacted a number of statutes designed to improve the federal rulemaking process, one of which is the Regulatory Flexibility Act of 1980, as amended (5 U.S.C. 601-612). Congress enacted RFA in response to concerns about the effect that federal regulations can have on small entities. According to SBA's Office of Advocacy, the major goals of the act are to (1) increase agency awareness and understanding of the impact of their regulations on small business, (2) require that agencies communicate and explain their findings to the public, and (3) encourage agencies to use flexibility and to provide regulatory relief to small entities.

RFA mandates certain actions on the part of agencies during the rulemaking process. For example, before publishing a proposed rule for which a notice of proposed rulemaking is required, sections 603 and 605(b) of the act state that a federal agency must prepare and make available for public comment an initial regulatory flexibility analysis that describes the anticipated effects of the proposed rule on small entities, unless the head of the agency certifies that the proposed rule will not have a "significant economic impact on a substantial number of small entities." Specifically, the act states that an agency's initial analysis must contain (1) a description of why the agency is considering the action; (2) the objectives and legal basis for the proposed rule; (3) a description and, where feasible, an estimate of the number of small entities to which the proposed rule will apply; (4) a description of the projected reporting, recordkeeping, and other compliance requirements of the proposed rule; and (5) a description of all federal rules that may duplicate, overlap, or

conflict with the proposed rule. The act also states that the initial analysis shall discuss significant alternatives for small entities that accomplish the objectives of applicable statutes, such as different compliance or reporting requirements, clarified or consolidated compliance and reporting requirements, and an exemption from coverage by the rule.

When a rule is promulgated that will have a significant economic impact on a substantial number of small entities, section 609(a) of RFA requires agencies to ensure that small entities have been given an opportunity to participate in the rulemaking process through the "reasonable use" of outreach techniques.[60] The act delineates a number of specific types of outreach techniques agencies could use, including (1) publishing the notice of proposed rulemaking in publications likely to be obtained by small entities, (2) directly notifying interested small entities, and (3) conducting open conferences or public hearings concerning the rule. Section 612 of the act requires the SBA Chief Counsel for Advocacy to monitor agencies' compliance with RFA and authorizes the Chief Counsel to appear as amicus curiae ("friend of the court") in court proceedings to review rules under the act.

FDA's Actions Met Basic RFA Requirements but Attracted Criticism

FDA determined that the proposed rule would have a significant economic impact on a substantial number of small entities. The agency concluded that a total of 80 small manufacturers and distributors would be affected by the proposed rule using (1) information in previous studies that indicated that 95 percent of all dietary supplement manufacturers were small businesses and (2) information from two market surveys that identified 85 manufacturers and distributors of dietary supplements suspected of containing ephedrine alkaloids. This determination triggered the requirement in sections 603 and 609 of the act, respectively, that FDA conduct an initial regulatory flexibility analysis and conduct outreach efforts.

Regulatory Flexibility Analysis Requirements

FDA's proposed rule addressed the basic elements that RFA requires agencies to include in an initial regulatory flexibility analysis. The rule described the reasons the agency was considering the action (market failure), stated the purpose and legal basis of the rule, described and

[60]FDA is not subject to other RFA requirements regarding small business participation, such as the requirement to convene small business advocacy review panels that the act, as amended by the Small Business Regulatory Enforcement Fairness Act, places on EPA and the Occupational Safety and Health Administration. For a discussion of these panels, see Regulatory Reform: Implementation of the Small Business Advocacy Review Panel Requirements (GAO/GGD-98-36, Mar. 18, 1998).

provided an estimate of the number of small entities to which FDA believed the rule would apply, and described the compliance requirements. In addition to describing direct compliance costs of between $3 million and $80 million, FDA also said that the proposed rule could have significant distributive effects in the form of reduced sales of as much as $230 million a year. FDA explicitly stated that costs and sales reductions of this magnitude might threaten the viability of many firms in this industry.

FDA also discussed significant alternatives to the proposed rule in the rule's regulatory flexibility analysis section, noting that most of the regulatory alternatives discussed in the cost-benefit analysis section would reduce the impact of this rule on small businesses. For example, FDA noted that taking no action or simply generating additional information would reduce the impact on small businesses to zero. However, FDA said that raising the proposed potency limit would have the same impact as the proposed rule and banning dietary supplements would have the greatest negative impact.

The industry representatives we met with confirmed that manufacturing and labeling of these products are generally limited to a relatively small number of manufacturing firms. Such firms would bear almost all of the expenditures required for compliance with the proposed rule. However, the executive director of one of the major trade associations we contacted pointed out that the proposed actions may also create some compliance costs for downstream distributors of the many different brands of products marketed. He said that these distributors might have to revise their marketing and promotional materials (for example, checking and revising claims and other information presented in the materials) to comply with the proposed rule. It is not clear whether FDA's estimated costs for relabeling also address this cost element.

In comments submitted on the proposed rule, SBA's Office of Advocacy was critical of FDA's initial regulatory flexibility analysis, stating that the underlying scientific data and analysis did not adequately support the proposed actions and the proposed rule did not provide enough information for someone to "meaningfully comment" on the proposed rule or alternatives. SBA also criticized FDA's analysis of the impacts on small businesses, saying it had underestimated the number of entities affected because it focused solely on the manufacturers of dietary supplements suspected of containing ephedrine alkaloids and did not take independent distributors into account. The Office of Advocacy noted that "many ephedra products are sold by tens of thousands of home-based distributorships that are part of multilevel marketing companies. Many of

these businesses, although part of a larger parent company, may nevertheless be independently owned and operated and considered to be 'small business concerns' under the Small Business Act." The office pointed out the importance of good information about the regulated industry, stating,

> In order to determine the impact of any regulation, an agency must make a reasonable effort to identify the type and number of entities likely to be affected by the regulation. This process of learning about the regulated industry not only helps the agency determine whether to certify a rule for regulatory flexibility purposes, it also helps the agency develop an analysis of impacts and choose appropriate regulatory alternatives that minimize economic burden.

In response to SBA's criticism, FDA officials told us that the agency need not consider the impact of its proposed rule on distributors of ephedrine alkaloids. The FDA officials cited several court decisions to support the proposition that, under RFA, an agency is under no obligation to conduct a small entity impact analysis of effects on entities that the agency does not regulate—that is, distributors.[61]

None of the major parties—FDA, SBA's Office of Advocacy, or industry associations—has information on the actual number of entities involved in the market for dietary supplements containing ephedrine alkaloids. Each acknowledge this as a limitation in attempts to analyze the effects of the proposed rule. FDA officials told us that the agency did not do a true market study for the proposed rule. The market review that FDA used in its analysis was done primarily for the purposes of informing the agency about supplements that might contain ephedrine alkaloids. SBA's Office of Advocacy recommended that FDA develop an outreach strategy to obtain more reliable industry data, and officials of both the Office of Advocacy and FDA noted that they have met on this issue since the comment period on the proposed rule ended. In addition, FDA officials said that they have contracted for a market study of the dietary supplement industry that should provide better information for future FDA analyses.

Outreach Efforts

With regard to the requirement in section 609(a) of the act requiring FDA to engage in outreach efforts, the regulatory docket shows that FDA provided opportunities during the development of the proposed rule for participation by affected businesses. For example, in addition to publishing the proposed rule, FDA published public notices and held public

[61]For example, United Distribution Cos. v. FERC, 88 F.3d 1105, 1170 (D.C. Cir. 1996).

meetings, during which industry representatives participated and provided testimony, and collected written comments on this issue. Representatives of industry trade associations also told us that FDA had placed notices about the proposed rule in the trade literature.

Unfunded Mandates Reform Act Requirements

The Unfunded Mandates Reform Act of 1995 imposes specific analytical requirements for certain rules that include a federal mandate that may result in the expenditure of $100 million or more by the private sector in any 1 year. FDA did not explicitly address UMRA in its proposed rule. However, FDA's economic analysis indicated that the direct expenditures imposed by this rule on the private sector would not rise to the level of $100 million and, thus, trigger the required additional analysis. Furthermore, even if the proposed rule did trigger UMRA's analytical requirements, FDA appears to have already satisfied most, if not all, of those requirements.

UMRA Requirements Apply Under Certain Circumstances

UMRA requires federal agencies to take certain actions during the rulemaking process for certain types of rules. For example, section 202 of UMRA requires agencies to provide a "written statement," including a qualitative and quantitative assessment of the anticipated costs and benefits for any proposed rule that includes a federal mandate that may result in the expenditure of $100 million or more by state, local, and tribal governments, in the aggregate, or by the private sector, in any 1 year.[62] Section 205 of the act states that, before promulgating any rule for which a written statement is required under section 202, agencies must identify and consider a reasonable number of regulatory alternatives and select the one that is the least costly, most cost-effective, or least burdensome alternative that achieves the objectives of the proposed rule. If the agency does not select the least costly, most cost-effective, or least burdensome option, and if the requirements of section 205 are not inconsistent with law, UMRA requires the agency head to publish with the final rule an explanation of why the least costly, most cost-effective, or least burdensome method was not adopted.

FDA's Proposed Rule Does Not Appear to Trigger Further Action Under UMRA

FDA's proposed rule did not mention UMRA. FDA officials said they did not include a specific UMRA section because the proposed rule was quite lengthy and they wanted to avoid adding any additional boilerplate. Our previous work on federal agency rulemaking indicated that even when their proposed rules do not trigger UMRA's analytical requirements, and although they are not required to do so, agencies sometimes include a

[62]Even if an agency's rule required $100 million in expenditures by the public or private sectors, UMRA's written statement requirements would only apply if the rule also imposed an "enforceable duty" that was not a condition of federal financial assistance or that did not arise from participation in a voluntary federal program. See Unfunded Mandates: Reform Act Has Had Little Effect on Agencies' Rulemaking Actions (GAO/GGD-98-30, Feb. 4, 1998).

brief statement to that effect explaining why they did not believe those requirements were applicable.[63]

Although FDA did not specifically mention UMRA, the agency's analysis of the costs associated with the proposed rule indicated that the rule would not result in expenditures of $100 million or more in any 1 year by the private sector. FDA estimated that the total compliance costs for the proposed action would be between $3 million and $80 million, with at most $70 million of those costs in the first year of implementation. These costs are primarily associated with relabeling and reformulating the affected supplements and appear to be expenditures covered by UMRA but do not rise to the $100-million threshold. Although FDA also estimated that the rule might result in lost sales for the dietary supplement industry of as much as $230 million per year, lost sales could not be considered direct expenditures by the private sector and, therefore, could not be used to trigger UMRA's analytical requirements.

SBA's Office of Advocacy contended that FDA overlooked the UMRA requirements. In the written comments submitted on FDA's proposed rule, the office stated, "If the agency had performed an adequate [cost-benefit] analysis, it would have been apparent that the economic impact of the instant rule would impose in excess of $100 million in costs to the industry." Officials from the Office of Advocacy told us that, if FDA properly estimated the number of affected businesses and the costs that would be imposed on those entities, FDA's estimate of expenditures by the private sector might increase to the level that would trigger UMRA's requirements. However, the Office of Advocacy could not provide any data showing that FDA had underestimated the number of manufacturers that would be affected by the relabeling and reformulation requirements in the rule or that FDA's cost estimates for those manufacturers were in error.

Even if the expenditures associated with the proposed rule had triggered UMRA's analytical requirements, FDA appears to have satisfied most if not all of those requirements. For example, FDA identified the provision of federal law under which the rule was being promulgated, quantitatively and qualitatively assessed the anticipated costs and benefits of the rule, and identified and considered a number of regulatory alternatives. Although FDA said that most of the regulatory alternatives would reduce the impact of the rule on businesses, FDA also indicated that these other options would not be as effective as the proposed rule.

[63]GGD-98-30 and Federal Rulemaking: Agencies Often Published Final Actions Without Proposed Rules (GAO/GGD-98-126, Aug. 31, 1998).

Comments From the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 30 1999

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Health, Education, and Human
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Dear Ms. Crosse:

Attached are Food and Drug Administration's proposed comments on the GAO draft report entitled, "DIETARY SUPPLEMENTS: Uncertainties in Analyses Underlying FDA's Proposed Regulation of Ephedrine Alkaloids," GAO/HEHS/GGD-99-90.

If we can be of further assistance, please call Lois Adams at (301) 827-0125.

Sincerely,

Melinda K. Plaisier
Interim Associate Director
for Legislative Affairs

Attachment

See comment 1.

Now on p. 23.

Now on pp. 23-24.

See comment 2.

Now on pp. 3 and 8.

Now on pp. 8-9.

See comment 3.

Now on pp. 3, 8, 10, and 12.

Comments of the Food and Drug Administration on the General Accounting Office Draft Report Entitled, "DIETARY SUPPLEMENTS: Uncertainties in Analyses Underlying FDA's Proposed Regulation of Ephedrine Alkaloids" GAO/HEHS/GGD-99-90

We appreciate the opportunity to review and comment on the draft report. We have, however, a number of serious concerns with the report as it is currently written. Most importantly, the draft report fails to acknowledge in the "Results in Brief" that the Food and Drug Administration (FDA) is justified in having concerns about the safety of dietary supplement products containing ephedrine alkaloids. A citation reflecting that acknowledgment does not appear until the "Conclusions" on page 30. FDA is concerned that not including this important finding in the "Results in Brief" not only weakens the assertion in the end of the report, but also may lead to the assumption that there is no real reason for the Agency to take action of any kind to regulate ephedrine alkaloid-containing products. We believe this is not GAO's intent. We strongly urge that the draft report be revised to incorporate in the "Results in Brief" section the conclusory statement (page 30 of the draft) that,

> "FDA was justified in determining that the number of AERs relating to dietary supplements containing ephedrine alkaloids warranted their attention and consideration of steps to address safety concerns. The available scientific information suggests that use of products containing synthetic ephedrine alkaloids can result in adverse experiences for some individuals and there are dosing recommendations for these OTC products."

A second major concern FDA has about the draft report is that it incorrectly that FDA relied principally on AER's in developing the proposed rule. See pages 3 and 10. This assertion is contrary to GAO's finding in the report that the scientific literature upon which FDA relied in the proposed rule indicates that the use of ephedrine alkaloids can result in serious cardiovascular and nervous system effects, including cardiomyopathy, stroke, seizure, psychosis, and myocardial necrosis. See pages 10 and 11.

Although FDA's initial concerns were triggered by the AER's, it was after evaluating the AER's together with the scientific literature and other data that FDA tentatively concluded that the risks attendant on consuming dietary supplements containing ephedrine alkaloids necessitated rulemaking to protect the public health. It appears that GAO is acknowledging that FDA is justified in taking action, but not some of the specific proposed actions. GAO should clarify that its concerns relate specifically and only to the data and information used by FDA to support the proposed serving and duration of use limitations, and not to the agency's finding of a significant public health risk or the other five proposed limitations on use in the proposed rule (e.g., label warnings, limitations on claims and against combinations with stimulants such as caffeine).

FDA is equally concerned about GAO's repeated assertions in the draft report that FDA relied solely on 13 AER's for determining that ephedrine alkaloids present unjustified hazards at low levels in the diet and establishing a specific serving level accordingly. See pages 3, 10, 13, 14,

15, and 17. FDA has repeatedly stated that the AER's were not the sole source upon which it relied to proposed the serving size found in the proposed rule. FDA relied on clinical studies that establish that 20 mg per serving of ephedrine present risks to some individuals. Furthermore, the scientific evidence on the individual variability to the effects of ephedrine and the data on the potential interactive effects from the mixtures of different ephedrine alkaloids, such as those contained in botanical sources of ephedrine alkaloids (e.g., Ephedra sinica), support that adverse events can be expected to occur in many individuals even with relatively low intakes, including intake levels lower than those used in the clinical studies.

See comment 4.

GAO's frequent statements in the draft report that FDA failed to exhibit a "causal analysis" linking ephedrine containing dietary supplements to the reported adverse events also distracts from GAO's overall conclusion that there is a significant public health concern that justifies agency action. See page 10 line 5, page 13 line 7, page 17 line 1, page 18 line 6 and page 31 line 14. Again, it appears that GAO acknowledges that FDA is justified in taking action, but not the action proposed concerning the serving and duration of use limitations. As stated above, our concern is that this ambiguity will be read to suggest that FDA was not justified in taking any action. We suggest that GAO revise the draft report to clarify its intent on this point.

Now on pp. 8, 11, 13, and 24.

See comment 5.

The draft report suggests that although FDA has used AER's along with available scientific information in several rulemakings, the use of AER's in this rulemaking in some respects, such as establishing an adulteration level, was unprecedented. However, GAO did not find that the use of AER's in developing a proposed rule of this type was in any way inappropriate or unscientific. GAO should clarify this fact.

See comment 6.

Because of the confusion that may be generated by the GAO report as it is currently written, we want to clarify the role that the AERs had in FDA's proposed action and the significance of the number and types of reports the Agency was receiving and continues to receive regarding products containing ephedrine alkaloids. To date, FDA has received about 1,000 AERs regarding products that contain or are suppected of containing ephedrine alkaloids.

Between 1993 and mid-1996, however, FDA received about 1,600 AERs associated with the use of dietary supplement products. Of these, over 800 AERs were associated with the use of dietary supplements that contained, or were suspected to contain, ephedrine alkaloids. As we stated in the proposed rule, "[t]hese adverse events tended to involve CVS [cardiovascular system] effects and NS [nervous system] effects. FDA evaluated the AERs showing CVS and NS effects and found that the single most common element was that the products contained, or were suspected to contain, a source of ephedrine alkaloids" (62 FR 30679).

FDA used the information available in the approximately 600 AERs, as of June 7, 1996, to describe patterns associated with these reports. A review of demographic information showed that in over half of the reported adverse events, the injured party was less than 40 years of age. Almost 75 percent of the adverse events were reported to occur in females, often using products

promoted for weight loss (62 FR 30682). About 59 percent of the adverse events were reported to occur within 4 weeks of starting to use the product. About 14 percent of the reported adverse events occurred on the first day of using the dietary supplement and, in a few cases, on the initial use. Overall, the reported signs and symptoms associated with these AERs included those where clinically serious events occurred, including heart attack, stroke, psychoses, seizure, and, in a few cases, death, as well as those with less clinical significance, including rapid and irregular heart rhythms, increased blood pressure, anxiety, nervousness, tremor, hyperactivity, and insomnia (62 FR 30683). With respect to the reports of less clinically significant effects, the Agency recognized that these reports could be an early warning of serious cardiovascular system (CVS) and nervous system (NS) risks if product use were to continue.

The information from the AERs also revealed consistent patterns of signs and symptoms in both healthy individuals and in those with underlying diseases or conditions. Many of these reported signs and symptoms occurred in young adults who generally would not have been expected to be at high risk for such conditions (e.g., heart attack and stroke). Included were the deaths of two young adult males in which the medical examiners attributed the cause of death to ephedrine toxicity (ARMS Nos. 10862 and 11134, summarized at 62 FR 30720 and 30722). In some cases, particular events appeared to reflect individual sensitivities related to dose levels, frequency, or duration of use of ephedrine alkaloids (62 FR 30684).

To better understand the nature and types of products associated with these AERs, FDA conducted a review of the marketplace (62 FR 30679). As discussed in the proposed rule, the Agency, over a 2-year period, collected over 25 dietary supplement products labeled as containing a known source of ephedrine alkaloids. The Agency found that the source of the ephedrine alkaloids in these supplements varied from the raw botanical to powdered plant material and concentrated extracts. Most of the products, however, contained concentrated extracts. FDA laboratories analyzed the products collected to quantify the levels of ephedrine alkaloids. Results of the analyses show that these products, taking into account the labeled recommended serving instructions, are likely to provide intakes of ephedrine alkaloids that range from below the detectable limits of FDA's analytical method to 110 milligrams (mg) per serving.

The ephedrine alkaloids are present in some products as a single ingredient, but more commonly they are combined with other ingredients, including vitamins, minerals, amino acids, and other botanicals. The majority of dietary supplements that contain ephedrine alkaloids also contain a source of xanthine alkaloids, e.g., caffeine which have a synergistic effect when combined with ephedrine alkaloids. Many of the dietary supplement products that FDA collected were promoted for uses such as weight loss, body building, increased energy, increased mental concentration, increased sexual sensations, or as an alternative to illicit street drugs.

FDA's evaluation included consideration of five questions:

(1) Are there consistent patterns of signs and symptoms associated with the use of a number of different ephedrine alkaloid-containing dietary supplement products?

FDA has tentatively concluded that there are consistent patterns of signs and symptoms associated with the use of a number of different ephedrine alkaloid-containing dietary supplement products (62 FR 30683). Sympathetic CVS and NS stimulant effects account for the majority of the reported adverse events associated with dietary supplements containing ephedrine alkaloids. These effects include heart attack, stroke, seizure, chest pain, psychosis, anxiety, nervousness, tremor, and hyperactivity. Importantly, specific types of adverse events did not appear to be limited to products promoted for any single use, such as weight loss, energy, or euphoria (62 FR 30683).

(2) Are the patterns of the signs and symptoms consistent with the available scientific evidence and known physiologic and pharmacologic effects of ephedrine alkaloids?

The Agency found that the patterns of the signs and symptoms of the adverse events are consistent with the available scientific evidence and known physiologic and pharmacologic effects of ephedrine alkaloids.[1]

The observed CVS and NS effects associated with the use of ephedrine alkaloid-containing dietary supplements are consistent with adverse events reported in controlled clinical trials using ephedrine in the treatment of obesity.[2] The unpredictability of individual responses to ephedrine alkaloid-containing dietary supplement products, as reported in the AERs, also is consistent with what is known about the physiological and pharmacological properties of these alkaloids.[3] Individual variability in the effects of ephedrine has been reported in several clinical investigations.[4] Several published reports in the scientific literature document that adverse events have occurred with traditional uses of ephedrine alkaloid-containing botanicals.[5]

(3) Is there sufficient evidence that the relationships are temporally correct, that is, does exposure occur temporally before the onset of the observed patterns of signs and symptoms?

FDA found evidence in the AERs of a correct temporal relationship between the use of the dietary supplements containing ephedrine alkaloids and the onset of the adverse events (62 FR 30689). The temporal relationship is considered to be correct when the adverse effects follow exposure.

(4) Is there other evidence of causality, even in the absence of controlled trials, e.g., evidence of dechallenge or positive rechallenge?

The Agency found that many of the AERs provided other evidence of a casual relationship between the ingestion of ephedrine alkaloids and the types of adverse events reported, including positive dechallenge and rechallenge (62 FR 30690).

(5) Considering the totality of the available information, is there a biologically plausible explanation for the adverse events?

FDA found that the data supported the biological plausibility of the types of adverse events reported in the AERs occurring with the use of ephedrine alkaloids (62 FR 30690). The observed adverse effects predominantly involve the CVS and NS and are consistent with the known physiological and pharmacological effects of ephedrine alkaloids noted in medical and scientific texts. Furthermore, similar patterns of effects have been documented in scientific literature reports and published results of controlled clinical trials using pharmaceutical preparations of various ephedrine alkaloids.

After having considered the totality of the available information, the Agency tentatively concluded in the proposed rule that, "there is a consistent, large, and growing body of evidence that establishes a causal association between the use of ephedrine alkaloids and subsequent adverse events" (62 FR 30691). The Agency also tentatively concluded that, "the use of ephedrine alkaloid-containing dietary supplements is associated with a serious and significant public health concern because of the nature of the adverse events and the size of the population at risk" (62 FR 30691). FDA now is evaluating its tentative conclusions in light of comments received on the proposed rule.

GAO RECOMMENDATION

Given the uncertainties in the information upon which FDA based its proposed rule, we recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to obtain additional information to support their conclusions regarding the specific requirements in the proposed rule before proceeding further with final rulemaking for dietary supplements containing ephedrine alkaloids. Specifically, FDA needs to provide stronger evidence on the relationship between intake of dietary supplements containing ephedrine alkaloids and the occurrence of adverse reactions to support the proposed dosing levels and duration of use limits.

FDA COMMENT

FDA believes it is critically important that the Agency address, in a scientifically defensible way, the public health and safety issues presented by the use of ephedrine alkaloid-containing dietary supplements. FDA agrees with GAO that the scientific issues for any final rule would be strengthened by the availability of additional information. Toward this end, FDA has already begun accumulating and reviewing data on more recent adverse events reported to the Agency since the publication of the proposed rule. After completing this latest round of investigation, laboratory testing, and analytical review, FDA will determine its degree of support for the requirements on the proposed rule or for alternative regulatory actions.

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GAO RECOMMENDATION

We also recommend that the Secretary direct the Commissioner to improve the transparency of FDA's cost-benefit analysis in the final rulemaking. Specifically, FDA should more fully explain the bases of its cost-benefit assumptions, the degree of uncertainty associated with those assumptions, and the implications of plausible alternative assumptions in the proposed action and other regulatory alternatives.

FDA COMMENT

We concur. While the Agency made a good-faith effort to explain clearly the bases of the assumptions used in the analysis and to disclose the degree of uncertainty associated with those assumptions, further reflection leads us to believe there is room for further clarification of the assumptions and basis for some of the elements of the cost-benefit analysis. FDA will take appropriate steps to correct the deficiencies of the cost-benefit analysis prior to publication of a final rule.

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GAO Comments

1. We have added language to the Results-in-Brief section of the report indicating that the number of AERs relating to dietary supplements containing ephedrine alkaloids warranted FDA's attention and consideration of steps to address safety concerns.

2. Throughout our report, we note that FDA used information from scientific literature to conclude that ingestion of ephedrine alkaloids can result in serious adverse events for some individuals. Our review of the scientific literature found case reports that suggest that ephedrine alkaloids could increase blood pressure in persons with normal and high blood pressure; predispose certain individuals to tachycardia (rapid heart rate); and cause cardiomyopathy (disease of the heart muscle), stroke, or myocardial necrosis (death of cells in the heart). We also found descriptions of adverse events associated with ephedrine alkaloids that affected the central nervous system, such as mania, paranoid psychoses, and seizures. However, FDA relied on AERs in establishing key components of its proposed rule—the serving and duration of use limits. We have clarified some language in the report to better reflect our concerns.

3. FDA highlighted in the proposed rule that clinical trials examining the efficacy of ephedrine to treat obesity had shown adverse events occurring at levels approaching 20 mg per serving. However, these trials did not provide information relating to adverse events below the 20 mg level. Thus, FDA did rely solely on results of tests performed on a small number of products implicated in 13 AERs to conclude that an 8 mg per serving level would be appropriate.

4. We note in our report that FDA did not perform an analysis on the AERs to determine which, if any, of the reported events were caused by dietary supplements containing ephedrine alkaloids. Further, we outlined several weaknesses inherent in any passive surveillance system, such as adverse event reporting. We continue to hold the view that without a causal link between the AERs and the ingestion of products containing ephedrine alkaloids, the exclusive use of AERs to support a specific dosing regimen is questionable.

5. FDA noted in its comments that we suggested that FDA's use of AERs in this rulemaking in some respects, such as establishing an adulteration level, was unprecedented. For this report, we examined whether the use of AERs for the proposed rule on dietary supplements containing ephedrine alkaloids was consistent with the use of AERs in prior rulemaking by FDA's Center for Food Safety and Applied Nutrition. We found that AERs had

been used in prior rulemaking, but they were used differently in this proposed rule when the agency relied solely on these reports to set a specific dosing level. However, we did not take a position on the appropriateness of the general use of AERs in rulemaking.

6. While we do not disagree with FDA's chronology of events detailed in pages 2-5 of its letter, we do not believe it is fully reflective of the role of the AERs in FDA's proposed action. In addition to using the AERs to signal a potential problem with products containing ephedrine alkaloids and to identify types of adverse events associated with such products, FDA also used the AERs as the key element in establishing the proposed dosing regimen.

Comments From the Small Business Administration

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

U.S. SMALL BUSINESS ADMINISTRATION
WASHINGTON, D.C. 20416

OFFICE OF CHIEF COUNSEL FOR ADVOCACY

APR 29 1999

William J. Scanlon
Director
Health Financing and
Workforce Issues
U.S. General Accounting Office
441 G Street, NW
Washington, DC 20548

Dear Mr. Scanlon:

Thank you for the opportunity to comment on the draft of the GAO Report on Uncertainties in Analyses Underlying FDA's Proposed Regulation of Ephedrine Alkaloids in Dietary Supplements. Our comments will address GAO's accurate assessment of FDA's deficient analysis, GAO's conclusion that FDA generally complied with the basic statutory and executive order requirements for rulemaking, and the issue of whether predictable indirect effects should be considered by lawmakers.

First and foremost, the Office of Advocacy would like to express appreciation for the forthright and in-depth assessment of FDA's analysis and scientific evidence in the dietary supplement proposal. GAO concluded that 1) FDA's analysis relied heavily on poorly documented reports of adverse events (AERs),[1] and 2) FDA's analysis of impacts was not transparent and did not fully reflect uncertainties in the underlying data and assumptions. Based on the demonstrable shortcomings of FDA's analysis, GAO is recommending that FDA go back and obtain additional information to support their conclusions before proceeding with a final rule, and also improve the transparency of the cost-benefit analysis in the final rule. These recommendations are reasonable in light of GAO's findings and will result in a more rational (and possibly less burdensome) regulation.

[1] With regard to AERs, GAO determined that:

- FDA used AERs differently in this rule than in previous rules,;
- the AERs have shortcomings (i.e., they are generally unreliable), and FDA's reliance on them adds uncertainty to the rule;
- the AERs were incomplete and inconsistent;
- FDA relied on AERs for setting dosing limits, but did not determine if these events were caused by Ephedra;
- there is weak support for FDA's proposed duration of use limitation; and
- FDA's estimate of the number and distribution of serious adverse events was poorly documented and could not be confirmed.

See comment 1.

Compliance with the Regulatory Flexibility Act

However, the Office of Advocacy finds one aspect of the report to be somewhat troublesome and confusing. Specifically, Advocacy does not understand the theory that an agency can fail to prepare an adequate analysis and, at the same time, comply with the requirements of the Regulatory Flexibility Act (RFA)[2] and other rulemaking requirements. GAO states,

> "We have concerns about the strength of the information upon which FDA based key elements of its proposal. In particular, FDA based its specific dosing level proposal on information associated with only 13 AERs, the quality of these AERs is questionable, and FDA did not establish a causal link between the ingestion of ephedrine alkaloids and the occurrence of these particular adverse events. Further, FDA based its estimate on the benefits of the proposed rule on the annual number of adverse events being reported to FDA prior to this rule. However, FDA did not document which AERs they identified as containing 'serious' events, and therefore, we could not determine the accuracy of FDA's estimated benefits. FDA has no internal guidance on the use of AERs for rulemaking related to foods and dietary supplements and used AERs differently in this proposed rule than in prior rulemaking . . . While FDA's conclusions regarding the desirability of the proposed action may be valid, we believe these conclusions are open to question because of limitations and uncertainties associated with the agency's scientific and economic analyses."

It seems counter-intuitive to suggest that such an inadequate analysis (as described above) could lead to the conclusion that FDA complied with the RFA. The premise of the RFA is to require that agencies consider fully the effects of their rulemaking on small entities. The key requirement of the RFA is the preparation of initial and final regulatory flexibility analyses to accompany, respectively, proposed and final rules that effect small businesses. If the analyses (and the facts/data/science underlying the analysis) do not have to be valid or supportable, then the analyses would be reduced to hollow procedural hoops through which agencies must jump on their way to implementing a rule, and the incentive to have rules based on fact would be eliminated.

The initial regulatory flexibility analysis (IRFA) is supposed to describe the impact of the proposed rule on small entities, the reasons why the action is being considered, its objectives and legal basis, the small entities affected, and significant alternatives to the proposed rule that may reduce burden on small entities while accomplishing the agency's stated objectives. The RFA does not identify specific analytical techniques an agency should use in discussing regulatory alternatives, but there is a guide in section 607 of the RFA that reads, "In complying with the provisions of sections 603 and 604 of this title, an agency may provide either a quantifiable or numerical description of the effects of a proposed rule or alternatives to the proposed rule, or more general descriptive statements

[2] 5 U.S.C. § 601 et seq.

if quantification is not practicable or **reliable**."[3] (Emphasis added). It is apparent that the RFA contemplates that agencies should not be guessing or using unreliable data.

Courts have taken the position that the various analyses required by the RFA must be adequate in order for a rule to be in compliance with the RFA. For instance, in *Southern Offshore Fishing Assoc. v. Daley*, 995 F. Supp. 1411 (M.D. Fla. 1998), the court remanded the RFA determinations of the National Marine Fishery Service (NMFS) with instructions to undertake a rational consideration of the economic effects and potential alternatives to the rule. On the issue of the agency's analysis, the court stated, "The record fails to contain an adequate explanation of the agency's calculation, if any, leaving no possibility to gauge its rationality, which is manifestly suspect."[4] The agency was ordered to redo its analysis and submit it to the court for review. Several months thereafter, dissatisfied with the court ordered RFA analysis, the court rebuked the agency again and appointed a special master to oversee the preparation of a proper RFA analysis.[5]

In this case, there is no way to determine—based on FDA's analysis—whether the benefits of the proposed rule exceed the costs. For instance, the agency never assessed the public health benefits of weight loss associated with the continued sale of the products. Conversely, the agency never assessed the costs to public health associated with putting thousands of distributors out of business. In this regard, the benefits outlined in the proposed rule may be over inflated. Nor did the agency adequately take into account the impact of over reporting that inevitably results from inaccurate publicity about alleged deaths. Over reporting could wipe out the benefits identified by the agency entirely.

The RFA requires public notice and comment on the analysis contained in the proposed rule.[6] In this case, the public cannot comment on vital aspects of the proposed rule because there is no rational basis for the cost-benefit analysis—nor is there transparency. In particular, the public cannot comment on the thirteen AERs on which the dosing limits are based because the public does not even know if the thirteen events were a result of ingesting a dietary supplement containing ephedrine.

The RFA is an outgrowth of the Administrative Procedure Act (APA). Both statutes require transparency and rationality in rulemaking. Failure to adhere to this fundamental requirement could easily be deemed arbitrary and capricious under either statute. There is a mountain of well-established case law that says the APA requires agencies to issue rational rules.[7] To determine whether the results of informal rulemaking meet that standard, the rulemaking record must support the factual conclusions underlying the rule, the policy determinations undergirding the rule must be rational, and the agency must

[3] 5 U.S.C. § 607.
[4] *Southern Offshore Fishing* at 1435.
[5] Order of Judge Steven D. Merryday Granting Plaintiff's Request for Special Master, *Southern Offshore Fishing*, (No. 97-1134-CIV-T-23C) (Oct. 16, 1998).
[6] 5 U.S.C. § 603(a).
[7] *Motor Vehicle Manufacturers Assoc. v. State Farm Mutual Automobile Insurance Co.*, 463 U.S. 29 (1983); *See Bowen v. American Hospital Association*, 476 U.S. 610, 643-45 (1986).

See comment 2.

adequately explain its conclusions.[8] FDA's rule is insufficiently transparent to determine if the three-prong test has been met.

Direct vs. Indirect Effects

The issue of whether an agency is required to prepare an analysis pursuant to the RFA when the impact is indirect (as opposed to direct) has been problematic. The Office of Advocacy is painfully aware of the court decisions stemming *from Mid-Tex Electric Cooperative, Inc. v. FERC*[9] that seem to state that agencies need not prepare an RFA analysis if the effects on an industry are indirect. Frankly, in spite of the dicta contained in *Mid-Tex*, the Office of Advocacy believes that the opposite is or should be the case. In any event, there is no law that says FDA must be constrained to agree with another agency's interpretation of the RFA—especially when there are such serious policy implications associated with putting thousands of legitimate businesses out of business.

It is difficult to fathom that destroying an entire industry by regulation is an indirect effect. In order to "comply" with FDA's rule, the industry would have to redirect its marketing strategies and materials if they were to remain in business. Even so, the quantities being sold would be severely reduced so as to eliminate profitability. The argument here is that some indirect effects are more indirect than others. Sometimes it is impossible to calculate every effect of a regulation. However, in this particular instance, the effects are grave and foreseeable. In fact, FDA acknowledged the foreseeability of the impacts in its proposed rule.

Finally, the Office of Advocacy is not aware of any comparable case law with respect to direct and indirect effects as it applies to Executive Order 12866. The executive order requires a cost-benefit analysis of all economically significant regulations and apparently does not distinguish between direct and indirect effects.[10] As such, the agency should have prepared an analysis of the impact on distributors of dietary supplements pursuant to

[8] *McGregor Printing Corp. v. Kemp*, 20 F.3d 1188, 1194 (D.C. Cir. 1994).

[9] 773 F.2d 327 (D.C. Cir. 1985). The court in *Mid-Tex* examined a challenge to a rule promulgated by the Federal Energy Regulatory Commission (FERC) that allowed public utilities to include current construction expenses in their rate bases. FERC maintained that the rule directly affected large public utilities only, and, as a result, would not have a significant impact on small entities. The agency, therefore, did not prepare a regulatory flexibility analysis. The challengers contended that the rule would raise electric rates and thereby adversely affect numerous small entities. In support of their contention, opponents cited statements by Senator Culver (one of the main sponsors of the Act) that both the direct and indirect effects of a rule must be considered as part of the analysis. *See* 126 CONG. REC. 21,558-59 (1980). The court disagreed with the challengers' interpretation of the RFA's legislative history and held that congressional intent with respect to the analysis of indirect effects was ambiguous.

[10] The executive order states that "Each agency shall tailor its regulations to impose the least burden on society, including individuals, businesses of differing sizes, and other entities (including small communities and governmental entities), consistent with obtaining the regulatory objectives, taking into account, among other things, and to the extent practicable, the costs of cumulative regulations." In addition, the executive order states, "'Significant regulatory action' means any regulatory action that is likely to result in a rule that may: (1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, the environment, public health or safety, or state, local, or tribal governments or communities..." Exec. Order No. 12866, 58 Fed. Reg. 51735 (1993), *reprinted in* 5 U.S.C. § 601.

the executive order. The executive order analysis would surely have satisfied the requirements of the RFA in spite of the controversy about indirect effects and the RFA.

In summary, the requirement for justifying a rule (iterated in the RFA, APA and Executive Order 12866) and the requirement to comply with the RFA and its analytical components cannot be compartmentalized--separating the two presents a legal conundrum. As the agency vested with sole responsibility for monitoring agency compliance with the RFA, Advocacy felt obliged to raise the issue. As for the issue of indirect effects, Advocacy believes its interpretation accords better treatment of the intent and purpose of the RFA.

Given the uncertainty surrounding the analysis of the dietary supplement proposal, a better alternative in the near term may be to allow states to regulate (as in Ohio) or to promulgate voluntary guidelines. Short of these recommendations, the Office of Advocacy concurs with GAO's recommendation to reanalyze the impacts of the proposed rule.

Again, we wish to express our gratitude for this opportunity to comment. Please do not hesitate to contact us directly if you have any questions at 202-205-6533.

Sincerely,

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5

GAO Comments

1. Although we did raise several concerns about specific parts of FDA's analysis and recommended certain revisions to any final rulemaking by FDA, we did not conclude that FDA failed to prepare an adequate analysis. RFA contains no standards or criteria that define an "adequate" analysis. The provisions of the act specify certain actions that an agency must take and certain elements that must be included in a regulatory flexibility analysis. Beyond those broad parameters, the act does not establish specific measures of quality or adequacy for an agency's analysis. Thus, we have no basis and are not in a position to make such a determination regarding the quality of FDA's analysis. Such a determination might be made if a specific rulemaking is judicially reviewed.[64] We did recognize, however, that FDA's analysis in the proposed rule contained the primary elements required under E.O. 12866, related OIRA guidance, and RFA.

2. We disagree with the Office of Advocacy's comments on direct versus indirect effects for three reasons.

- First, prior case law indicates that agencies need not take the indirect effects of their rules into account when conducting a regulatory flexibility analysis. Most recently, in a May 14, 1999, decision, the U.S. Court of Appeals for the District of Columbia Circuit said, "we have consistently interpreted the RFA . . . to impose no obligation upon an agency 'to conduct a small entity impact analysis of effects on entities which it does not regulate.'"[65] The court also quoted Mid-Tex in noting, "Congress did not intend to require that every agency consider every indirect effect that any regulation might have on small businesses in any stratum of the national economy."[66] The court also rejected the petitioners' contention that it must defer to the interpretations of SBA's Chief Counsel for Advocacy regarding RFA, pointing out that SBA "neither administers nor has any policymaking role under RFA; at most its role is advisory . . . . Therefore, we do not defer to the SBA's interpretation of the RFA."[67]
- Second, we do not believe that it is logical to conclude that the absence of case law comparable to Mid-Tex with respect to direct and indirect effects

[64]The Small Business Regulatory Enforcement Fairness Act of 1996 amended RFA to provide for judicial review of an agency's compliance with RFA.

[65]American Trucking Associations, Inc., et al, v. United States Environmental Protection Agency, No. 97-1440 U.S. App. LEXIS 9064, at *40 (D.C. Cir. May 14, 1999), citing Motor & Equip. Mfrs. Ass'n. v. Nichols, 142 F.3d 449, 467 & n.18 (1988).

[66]American Trucking, 1999 U.S. App. LEXIS 9064, at *41.

[67]American Trucking, 1999 U.S. App. LEXIS 9064, at *42. The court referred to 5 U.S.C. sections 601(3), 602(b), 603(a), 605(b), 609(b)(1), and 612 and Scheduled Airlines Traffic Offices, Inc. v. Department of Defense, 87 F.3d 1356, 1361 (D.C. Cir. 1996) (no deference owed to agency interpretation of statute it does not administer).

as they apply to E.O. 12866 means that FDA should have prepared an analysis of the rule's impact on distributors. The absence of case law says nothing about FDA's analytical obligations under the executive order.

- Third, we believe that, by estimating total lost sales to the industry if the proposed rule or other regulatory alternatives were implemented, FDA identified the potential magnitude of impacts on distributors in both its cost-benefit analysis and regulatory flexibility analysis. FDA identified such lost sales as a distributive effect, rather than a true social cost, because the loss only represents a transfer of resources within society (more for consumers and less for the dietary supplement industry). In addition, the total loss to the industry is the total loss to the industry; it should not be double counted—once for manufacturers and again for distributors—in a cost-benefit analysis. Finally, FDA explicitly acknowledged in its proposed rule that such effects would be significant to affected parties and could threaten the viability of many firms in this industry.

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In addition to those named above, Tim Bober, Curtis Copeland, Marcia Crosse, Carolyn L. Feis, and Kurt Kroemer made key contributions to this report.

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