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4327 02P-0120

April 26, 2002

Tommy Thompson, Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Re: *Comments in Opposition to Request to Ban Meridia®*
(FDA Docket No. 02P-0120/CP1)

Dear Secretary Thompson:

Abbott Laboratories ("Abbott") is writing to oppose the above-referenced petition submitted by Public Citizen Health Research Group ("HRG" and the "Petition") on March 19, 2002. In its Petition, HRG requests withdrawal of approval and immediate suspension from the market of the prescription drug product Meridia® (sibutramine hydrochloride monohydrate). ^{1/}

Abbott manufactures and markets Meridia under a new drug application ("NDA") approved by the Food and Drug Administration ("FDA"). Meridia has been studied extensively and thoroughly in more than one hundred clinical trials involving over 12,000 patients. Worldwide, an estimated 8.5 million people in seventy countries have used sibutramine since the drug first gained approval in 1997. Meridia has a strong record of safe use and demonstrated efficacy in weight loss and weight maintenance. Weight loss and weight maintenance have been shown to lower the risk of obesity-related conditions such as cardiovascular disease and type 2 diabetes. Based on the facts developed below, we stand fully behind Meridia as a safe and effective treatment for obesity and long-term weight management.

The Petition provides no basis—factual or legal—to support HRG's extraordinary request that FDA withdraw its approval of Meridia, much less the

^{1/} Sibutramine is marketed in the United States under the trade name Meridia and in Europe under the trade names Reductil®, Reduxade®, Ectiva®, and Zeliuim®. These comments refer to the drug as "Meridia" or "sibutramine."

demand that the Secretary ban Meridia as an imminent hazard to public health. In addition, HRG has misrepresented the role of Meridia in the treatment of obesity. The Petition ignores the fact that obesity is both a serious medical condition with grave health risks as well as a serious public health issue of epidemic proportions. It omits any discussion of the specific steps taken by FDA to ensure the safe and effective use of Meridia. It ignores pivotal information demonstrating the safety and effectiveness of the drug product.

HRG's misrepresentation of the safety and efficacy of Meridia, via widespread media publicity, has created undue alarm among physicians and patients who rely on Meridia to treat a serious medical condition with limited treatment options. Abbott submits these comments to ensure swift denial of the Petition and to otherwise set the record straight. 2/

I. EXECUTIVE SUMMARY

Obesity is a worldwide public health problem, afflicting more than 250 million people. More than sixty percent of the adult population in the United States is overweight or obese and the numbers are growing steadily. It is estimated that 300,000 deaths annually in the United States may be attributed to obesity. Aside from an increased risk of death, obese patients have an increased risk of hypertension, stroke, type 2 diabetes mellitus, coronary heart disease, gallbladder disease, osteoarthritis, sleep apnea and other respiratory problems, and certain types of cancer. *See* Section II.A. and II.B., below.

Meridia is one of only two drugs approved by FDA for the treatment of obesity and long-term weight management. The product offers important benefits to appropriate patients who, without the assistance of pharmacotherapy, are unable to manage their weight and improve their overall risk profile. Multiple randomized, controlled clinical trials demonstrate that patients treated with Meridia can lose at least five percent of their body weight. A large body of research confirms that by maintaining weight loss of five to ten percent of body weight, an individual significantly reduces his or her risk of obesity-related conditions, including high blood pressure, insulin resistance, lipid abnormalities, decreased lung function, osteoarthritis, type 2 diabetes, and coronary heart disease. *See* Sections II.B. and II.C., below.

2/ By submitting these comments Abbott does not waive any right it has to the confidentiality of data or information contained in any of its submissions to FDA, including the NDA and the investigational new drug ("IND") application for Meridia. *See* 21 U.S.C. § 331(j); 5 U.S.C. § 552(b)(4); 21 C.F.R. § 20.61.

Withdrawal of an approved drug product such as Meridia requires, among others, an affirmative finding that the drug is unsafe for its approved uses. *See* Section III, below. The Petition falls far short of establishing any unexpected safety issues, let alone presenting evidence that would justify undoing FDA's carefully considered approval of the drug. The Petition is an exercise in rhetorical misdirection, not thoughtful science.

First, the Petition presents a selective and misleading view of the FDA approval process for Meridia, omitting significant steps taken by FDA reviewers and senior officials within the Center for Drug Evaluation and Research to assure the safety and effectiveness of Meridia. *See* Section IV.A., below.

Second, the claims made by HRG about the efficacy of Meridia are neither factual nor objective. The data that formed the basis for the NDA approval, complemented by subsequent studies published in the peer-reviewed literature, demonstrate the important clinical role played by Meridia. In these studies, patients treated with Meridia achieved mean weight loss ranging from nine pounds to over twenty pounds. Data also show maintenance of substantial weight loss among sibutramine patients for up to two years. The results from these controlled clinical trials have been confirmed in subsequent studies performed in community practice settings involving thousands of patients. Overall, the body of efficacy data is consistent, robust, and of scientifically proven clinical relevance. *See* Section IV.B., below.

Similarly, HRG's safety concerns are readily refuted by the extensive integrated safety database of Meridia drawn from more than 60 clinical studies, and by the worldwide post-marketing surveillance conducted since approval in late 1997. At the approved doses of Meridia, mean increases in blood pressure and heart rate are minor, and are ameliorated by accompanying weight loss. These effects are appropriately and responsibly addressed in the product labeling. Importantly, in controlled clinical trials, the incidence of events such as myocardial infarction, myocardial ischemia, heart failure, cardiomyopathy, and stroke are statistically indistinguishable from placebo-treated patients. Furthermore, in the post-market setting in which more than 8.5 million patients have received Meridia, the estimated fatality rate is nearly 200-fold lower than that reported for an obese population. *See* Section IV.C., below.

These facts and scientific analyses reaffirm that informed physicians should continue to regard Meridia as a safe and effective treatment option in the management of a serious medical condition and that physicians should continue to prescribe the drug as recommended in the approved labeling. Removal of Meridia would, for all intents and purposes, force many obese patients to go untreated or, even worse, cause many to use unproven and potentially dangerous fad remedies.

II. BACKGROUND

A. The Obesity Pandemic

Obesity is a worldwide health problem of epidemic proportion. Over 250 million adults are obese and many more are overweight. ^{3/} The World Health Organization (“WHO”) has declared obesity “one of today’s most blatantly visible—yet most neglected—public health problems.” ^{4/} As such, the consequences of this chronic disease may soon replace traditional public health concerns such as malnutrition or infectious disease as one of the most significant contributors to illness. ^{5/}

In the United States, the Surgeon General in 2001 identified obesity as a national priority for treatment, citing results from the 1999 National Health and Nutrition Examination Survey that approximately 61% of adults in the United States are overweight or obese. ^{6/} And, the numbers are growing: obesity among U.S. adults aged 20-74 years has nearly doubled from approximately 15% in 1980 to an estimated 27% in 1999. ^{7/}

B. The Consequences of Obesity

Foremost, obese patients are at a significantly increased risk for premature death. In the United States, approximately 300,000 deaths per year

^{3/} World Health Organization, *Obesity: Preventing and Managing the Global Epidemic*, Technical Report Series 894 at 3, 4 (2000) (“WHO 2000”). Abbott submits herewith the references upon which it relies, arranged alphabetically for the reader’s convenience.

^{4/} World Health Organization, *Controlling the Global Obesity Epidemic*.

^{5/} WHO 2000 at 1-2.

^{6/} U.S. Department of Health and Human Services, *The Surgeon General’s Call to Action to Prevent and Decrease Overweight and Obesity 2001* at xiii (2001) (“HHS 2001”).

^{7/} Centers for Disease Control and Prevention, National Center for Health Statistics, *Obesity and Overweight: A Public Health Epidemic*.

may be attributed to obesity. ^{8/} Mortality begins to increase with BMI >25. ^{9/} For persons with a BMI of 30 or above, premature death from all causes is increased by 50-100% above that of persons with a BMI in the range of 20-25. ^{10/}

The increase in mortality rates is primarily associated with obesity-related cardiac and vascular complications. Significantly increased risk of death from cardiovascular disease was noted in women with a BMI greater than 25.0 and in men with a BMI greater than 26.5. ^{11/} According to the Nurses' Health Study— involving 115,195 women followed over a period of 16 years—the risk of death was 60-70% higher among subjects with a BMI between 29-32 compared to subjects with a BMI between 25 and 27. ^{12/}

Although obesity is a disease in its own right, it is also a key risk factor for hypertension, stroke, type 2 diabetes mellitus, coronary heart disease, gallbladder disease, osteoarthritis, sleep apnea, other respiratory problems, and certain types of cancers (e.g., endometrial, breast, prostate, and colon). More specifically,

- *Coronary Heart Disease (CHD)*. The risk of CHD is proportionate to the degree of overweight. This risk is higher in younger patients and patients with greater abdominal adiposity. ^{13/}

^{8/} Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, *The Burden of Chronic Diseases and Their Risk Factors: National and State Perspectives 2002* (2002).

^{9/} See National Institutes of Health, *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* at 18 (2000) ("NIH Practical Guide"). Throughout this document, we refer to two measures of body fat: the body mass index (BMI) and waist circumference. BMI is an arithmetic function of the patient's weight and height expressed as weight in kilograms divided by height in meters squared. NIH has defined *overweight* as a BMI of 25-29.9 kg/m² and *obesity* as a BMI \geq 30 kg/m². See *id.* at 1. Waist circumference is a tool to evaluate abdominal adiposity. A circumference of greater than 40 inches in men and greater than 35 in women is associated with high-risk for diabetes, dyslipidemia, hypertension, and cardiovascular disease. See *id.* Abdominal adiposity is associated with greater cardiovascular risk than gluteal-femoral fat and may be an independent risk predictor. *Id.* at 10 (table showing classification of overweight and obesity in adults according to BMI, waist circumference and associated disease risk).

^{10/} HHS 2001 at 8.

^{11/} E. Calle et al., *Body-Mass Index and Mortality in a Prospective Cohort of U.S. Adults*, 341 NEW ENGL. J. MED. 1097, 1101 (1995).

^{12/} J.E. Manson & G.A. Faich, *Pharmacotherapy for Obesity – Do the Benefits Outweigh the Risks?* 333 NEW ENGL. J. MED. 659 (1996).

^{13/} WHO 2000 at 47.

- *Hypertension.* The prevalence of high blood pressure in adults with BMI greater than or equal to 30 is 38.4% for men and 32.2% for women, ^{14/} and the risk of hypertension increases with the duration of obesity. ^{15/} Abdominal adiposity also is a hypertension risk factor. ^{16/}
- *Type 2 Diabetes Mellitus.* The prevalence of type 2 diabetes has tripled in the past 30 years in parallel with the upsurge in obesity. ^{17/} In one study, weight gain of 15.4-22 lb. after 18 years of age correlated to a two-fold increase in risk of diabetes, and an adult BMI ≥ 31 correlated to a 40-fold risk increase. The relative risk increased by about 25% for each additional unit of BMI >22 . ^{18/}
- *Stroke.* Current data from several studies suggest a relationship between obesity or abdominal adiposity and risk of stroke. ^{19/} In one, a weight gain of 24-44 lb. increased the risk of ischemic stroke by 69%, and weight gain of over 44 lb. increased the risk of ischemic stroke by 152%. ^{20/}
- *Thrombosis/Embolism.* Obesity is a risk factor for pulmonary embolism and predisposes patients to venous stasis and deep vein thrombosis, the antecedents of most cases of pulmonary embolism. ^{21/} Morbid obesity is a major risk factor in cases of sudden death from postoperative acute pulmonary embolism. ^{22/}

^{14/} National Heart, Lung, and Blood Institute, *Hypertension: Guidelines on Overweight and Obesity* (Electronic Textbook).

^{15/} WHO 2000 at 47-48 (the risk of hypertension increases with the duration of obesity).

^{16/} See WHO 2000 at 39.

^{17/} National Institute of Diabetes, Digestive & Kidney Diseases, NIH, News Brief, *Diet and Exercise Dramatically Delay Type 2 Diabetes: Diabetes Medication Metformin Also Effective* at 4 (Aug. 8, 2001).

^{18/} G.A. Colditz et al., *Weight Gain As a Risk Factor for Clinical Diabetes Mellitus in Women*, 122 ANNALS INTERNAL MED. 481, 484 (1995).

^{19/} WHO 2000 at 48; K.M. Rexrode et al., *A Prospective Study of Body Mass Index, Weight Change, and Risk of Stroke in Women*, JAMA 1539, 1541 (1997).

^{20/} See Rexrode at 1544, tbl. 3.

^{21/} S. Goldhaber et al., *A Prospective Study of Risk Factors for Pulmonary Embolism in Women*, 277 JAMA 642, 644 (1997).

^{22/} H. Blaszyh and J. Bjornsson, *Factor V Leiden and Morbid Obesity in Fatal Postoperative Pulmonary Embolism*, 135 ARCHIVES SURGERY 1410, 1413 (2000).

- *Gallbladder Disease.* Gallstones occur 3-4 times more often in obese patients and this risk increases with abdominal adiposity. 23/
- *Osteoarthritis.* Obesity is associated with the development of osteoarthritis and gout. Factors may include mechanical stresses of increased weight, metabolic changes from increased weight and abdominal adiposity, and dietary content. 24/
- *Sleep Apnea.* Obese patients compose 65-75% of patients with obstructive sleep apnea. 25/ Sleep apnea has been reported in 25% of obese patients. 26/
- *Cancer.* Obese women are at greater risk for breast, endometrial, ovarian, and cervical cancer, and obese men may have an increased risk of prostate cancer. 27/

Finally, the economic impact of overweight and obesity is profound. In the United States in calendar year 2000 alone, the direct and indirect costs of obesity totaled \$117 billion, 28/ based primarily on the consequences of type 2 diabetes, coronary heart disease, and hypertension. Modest weight loss, however, has been shown to reduce these effects and, in turn, the associated costs. Two recently published large, prospective randomized studies—the Finnish Diabetes Prevention Study and the Diabetes Prevention Program—independently demonstrate that overweight patients who lose approximately 5% of their body weight reduce their risk of developing type 2 diabetes by 58%. 29/ Weight reduction

23/ WHO 2000 at 50.

24/ WHO 2000 at 54-55.

25/ *Id.* at 55.

26/ See O. Resta et al., *Sleep-Related Breathing Disorders, Loud Snoring and Excessive Daytime Sleepiness in Obese Subjects*, 25 INT'L J. OBESITY 669, 672 (2001).

27/ WHO 2000 at 48.

28/ HHS 2001 at 10.

29/ Diabetes Prevention Program Research Group, *Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin*, 346 NEW ENGL. J. MED. 393, 393 (2002); see also J. Tuomilehto et al., *Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle Among Subjects with Impaired Glucose Tolerance*, 344 NEW ENGL. J. MED. 1343, 1348 (2001).

of any amount in women who had never smoked, 40-60 years of age, reduces all-cause mortality by 20% and diabetes-associated mortality by 30-40%. ^{30/}

C. Treating Obesity

Obesity is a chronic disease and treatment is a lifelong effort. ^{31/} According to the CDC's Behavioral Risk Factor Surveillance System, 80% of overweight participants and 87% of obese participants claimed they were trying to lose or maintain their weight. ^{32/} Of the participants trying to lose or maintain weight, 16% of overweight participants and 43% of obese participants had not sought professional advice on weight management. ^{33/} Instead, many obese individuals resort to potentially dangerous, unsupervised methods to induce weight loss, such as diet pills, skipping meals, dietary supplements, and fad diets. ^{34/}

The treatment of obesity, according to NIH guidelines, requires a comprehensive program that includes diet, increased physical activity, and behavioral therapy. ^{35/} In addition, NIH specifically recognizes the use of FDA-approved pharmacotherapy in qualified patients, particularly those high-risk patients who have not achieved clinically significant weight loss after six months of "lifestyle changes." ^{36/}

D. Meridia

Meridia is one of only two prescription drug products approved for long-term use in treating obesity. ^{37/} Approved by FDA in 1997, Meridia is

^{30/} See D.F. Williamson et al., *Prospective Study of Intentional Weight Loss and Mortality in Never-Smoking Overweight U.S. White Women Aged 40-64 years*, 141 AM. J. EPIDEMIOLOGY 1128, 1135 (1995).

^{31/} See NIH Practical Guide at 1.

^{32/} See National Center for Chronic Disease Prevention and Health Promotion, CDC, *Obesity and Overweight: Obesity Trends*.

^{33/} See *id.*

^{34/} See, e.g., *Losing Weight: More Than Counting Calories*, FDA Consumer Magazine (Jan.-Feb. 2002) ("FDA Consumer, Losing Weight") (cautioning consumers about the use of dietary supplements marketed for weight loss and the dangers for persons with certain conditions and for interactions with drugs).

^{35/} NIH Practical Guide at 2-3.

^{36/} *Id.* at 3.

^{37/} FDA has approved four other drugs for the short-term treatment of obesity: Bontril (phendimetrazine tartrate), Desoxyn (methamphetamine hydrochloride), Ionamin (phentermine resin), Adipex-P (phentermine hydrochloride). See FDA Consumer, *Losing Weight* at 7; see generally

indicated for the management of obesity, including weight loss and maintenance of weight loss, in conjunction with a reduced-calorie diet. It is labeled only for patients with an initial body mass index of at least 30 (for example, a person 5' 9" tall weighing 203 pounds), or an initial body mass index of at least 27 (for example, a person 5' 9" tall weighing 182 pounds) who have other risk factors, such as hypertension, diabetes, or dislipidemia. ^{38/}

Meridia is a serotonin and norepinephrine reuptake inhibitor ^{39/} that acts centrally to reduce energy intake by inducing a feeling of fullness (or satiety) after eating, and affecting energy expenditure. ^{40/} It is marketed in capsule form for oral administration and must be used under the supervision of a physician. ^{41/}

Among the warnings and contraindications in the FDA-approved labeling, physicians are instructed that "Meridia substantially increases blood pressure in some patients" and that "[r]egular monitoring of blood pressure is required when prescribing Meridia." ^{42/} The labeling also states that Meridia has been associated with increased heart rate and blood pressure and, therefore, "should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke." ^{43/}

When used in accordance with these and other specific admonitions, and in accordance with instructions on proper dosing and administration, Meridia

Footnote continued:

S.Z. Yanovski & J.A. Yanovski, *Obesity*, 346 NEW ENGL. J. MED. 591 (2002). Only Bontril, Ionamin, and Adipex-P are currently marketed. The labeling for each of these drugs defines short-term treatment as "a few weeks." All four drugs are classified as "anorectics" or "anorexigenics." All four function by central nervous system stimulation and elevation of blood pressure. Desoxyn is a member of the amphetamine group of sympathomimetic amines, while Bontril, Ionamin, and Adipex-P consist of sympathomimetic amines with pharmacological activity similar to amphetamine. See generally 56 Physicians' Desk Reference (2002).

^{38/} Meridia Labeling ("Meridia Labeling"), Indications and Usage.

^{39/} *Id.*, Mode of Action, Clinical Pharmacology.

^{40/} D.L. Hansen et al., *The Effect of Sibutramine on Energy Expenditure and Appetite During Chronic Treatment Without Dietary Restrictions*, INT'L J. OBESITY 1016 (1999).

^{41/} Xenical® (orlistat) is the only other obesity-treatment drug that is approved for a treatment period longer than "a few weeks." Xenical is a lipase inhibitor that inhibits the absorption of dietary fats. It is associated with gastrointestinal side effects and discomfort. See Xenical Physician Labeling.

^{42/} Meridia Labeling, Warnings.

^{43/} *Id.*

has been determined by FDA to be safe and effective for the promotion of weight loss. FDA's determination is supported by substantial evidence of effectiveness consisting of 11 well controlled clinical trials, including 3 pivotal studies of at least 6 months duration. ^{44/} The FDA's determination that Meridia is safe was based upon an integrated safety database that contained all safety data collected in over 60 clinical studies.

III. LEGAL FRAMEWORK

Meridia is a "new drug" under section 201(p) of the Food, Drug, and Cosmetic Act (the "FDCA") and, as such, may be marketed in interstate commerce only if it is the subject of an approved application under section 505(b) or 505(j) of the FDCA. In November 1997, FDA approved the marketing of Meridia based on an NDA submitted under section 505(b).

Following approval of a new drug, the Secretary and, by delegation of authority, the Commissioner of Food and Drugs, is authorized to withdraw approval only if the Commissioner makes one of the specific findings in section 505(e) of the FDCA. Thus, FDA may withdraw an NDA only if it concludes, among others:

- that clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application was approved,
- that new evidence of clinical experience evaluated together with the evidence available to the Secretary when the application was approved shows that the drug is not shown to be safe for use under the approved conditions of use, or
- that new information evaluated together with the evidence available when the application was approved indicates that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. ^{45/}

^{44/} See *id.* Clinical Studies.

^{45/} See 21 U.S.C. § 355(e)(1)-(3).

These and other such findings must be made only “after due notice and opportunity for hearing to the applicant.” ^{46/}

HRG has not only requested withdrawal of the NDA, it has also demanded that the Secretary “immediately ban” Meridia. To take this extraordinary step, the Secretary must find that the drug presents “an imminent hazard to the public health.” ^{47/} This authority applies “only in the exceptional case of an emergency, which does not permit the Secretary to correct it by other means.” ^{48/} To underscore the seriousness of the remedy, the law rests this decision solely with the Secretary; it cannot be delegated to FDA or to any other official.

None of the statutory bases for withdrawal is remotely applicable to Meridia. As shown below, clinical data already reviewed by FDA, and new data generated subsequent to approval, continue to demonstrate the safety and effectiveness of the drug. All drugs have risks, but those presented by sibutramine therapy can be managed safely. ^{49/} Use of Meridia certainly does not present an irreparable hazard to public health. To the contrary, the drug provides a safe and effective treatment for a pernicious health problem that, presently, has few viable treatment options.

IV. DISCUSSION

HRG falls far short of raising a plausible legal or medical issue associated with the use of Meridia. The reason is plain: when used in appropriate patients according to the FDA-approved labeling, Meridia is a safe and effective tool in the treatment of obesity and long-term weight management.

HRG’s argument centers on a selective discussion of the FDA review process to suggest that the agency’s approval decision lacked rigor. As shown below, nothing could be further from the truth. HRG ignores—intentionally or otherwise—publicly available information showing that FDA’s review of Meridia was comprehensive in its analysis of the data, thorough in addressing issues raised by the advisory committee, and responsible in its actions to manage the very risks about which HRG now complains.

^{46/} 21 U.S.C. § 355(e).

^{47/} 21 U.S.C. § 355(e).

^{48/} Sen. Rep. No. 1744 at 7, 87th Cong., 2d Sess. (1962).

^{49/} FDA, *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*, at 21-22 (May 1999).

Second, the Petition dismisses the efficacy of Meridia, despite ample data in the NDA and the post-market literature showing that patients using Meridia achieve clinically significant weight reduction and long-term maintenance. Finally, HRG's claims about the safety of Meridia are, again, the product of reactive rather than rational analysis. The safety of Meridia is supported by an extensive integrated safety database representing over 60 clinical studies complemented by a worldwide post-marketing surveillance program. In all, the Petition urges an extreme remedy based on few facts and no coherent analysis.

A. The Petition Misrepresents the FDA's Review of Meridia

FDA's approval of Meridia was based on an extensive pre-market review process, including multi-disciplinary analysis by experts within the Division of Metabolic and Endocrine Drug Products (the "Division"), advisory committee consideration, post-advisory committee dialogue with the sponsor and, finally, senior-level review and approval by the Division and by the supervising Office.

The Petition fails to acknowledge substantial regulatory review activities, occurring after the Advisory Committee meeting, that led to the approval of the Meridia NDA on November 22, 1997. During this time, Knoll Pharmaceutical Company ("Knoll"), ^{50/} the sponsor of the original NDA for Meridia, incorporated substantive changes into the final FDA-approved labeling, changed the available strengths of the drug, developed a Patient Information Insert to help ensure proper patient use, and put forward a plan for continued post-market study. The petition also ignores the accumulated safety and efficacy information gathered since approval that takes into account broad patient exposure, including the results of a long-term study now incorporated into the Meridia labeling.

1. August 1995 through September 1996

Knoll submitted the NDA to FDA for review on August 7, 1995. Early in the agency review, one member of the Division's review team raised concerns regarding increases in blood pressure associated with sibutramine. To help assess these concerns, the Division requested a "consult" from the Division of Cardio-Renal Drug Products. Based on review of the blood pressure data for sibutramine, the

^{50/} Abbott purchased Knoll in 2001.

Cardio-Renal Division Director, Dr. Raymond Lipicky, concluded that this data did not warrant rejecting the NDA. ^{51/} As Dr. Lipicky stated:

one could evolve a risk/benefit analysis (gain from weight loss vs risk of stroke) . . . and that decision making should be based upon such an analysis. Consequently, although sibutramine raises blood pressure (and that is clear from the data reviewed . . .) that fact alone is an insufficient cause for rejecting sibutramine as an appropriate anti-obesity agent. ^{52/}

Clearly, FDA was aware of the effect of Meridia on blood pressure and weighed those risks against the benefits from weight loss—an analysis that HRG ignores in its entirety.

On September 26, 1996, the Advisory Committee met to consider the Meridia NDA. This meeting was based on the drug and labeling as presented in the original submission by Knoll. The Committee concluded that Meridia met the criteria for effectiveness for this class of drugs as established by FDA in its “Guidance for the Clinical Evaluation of Weight-Control Drugs.” ^{53/} The Committee also concluded that while the blood pressure effect of Meridia is clinically important, its clinical significance had not been fully explored. ^{54/} Finally, the Committee was closely divided on whether the benefits of Meridia outweighed the risks based, again, on the original submission. ^{55/}

2. November 1996 through November 1997

Following the Advisory Committee meeting, representatives from Knoll and the Division discussed the issues raised during the Meridia review process. On November 8, 1996, based in part on commitments made by Knoll, the Director of the Office of Drug Evaluation II issued an “approvable” letter for

^{51/} See Memorandum from the Director of the Division of Cardio-Renal Drug Products, FDA, HHS, to Maureen Hess and Eric Colman, Division Metabolic and Endocrine Drug Products, FDA, at 1 (Sept. 18, 1996).

^{52/} *Id.* at 1.

^{53/} See Endocrinologic and Metabolic Drugs Advisory Committee, FDA, Meeting Transcript 238, 268-69, 280-81 (Sept. 26, 1996) (“Advisory Committee Transcript”).

^{54/} *Id.* at 238, 249-50, 269-70, 281.

^{55/} *Id.* at 238, 270-73, 281.

Meridia that contained requests for additional work, including further analyses of blood pressure data. 56/

As Dr. Sobol, the Metabolic and Endocrine Drug Products Division Director, stated, "during the next several months we hope to refine methods of blood pressure screening by careful reanalysis of existing data." 57/ Other actions included eliminating the 20 mg dose, development of a Patient Information Insert, and suggestions for a possible Phase IV commitment. As Dr. Sobol concluded, "I believe that this approach would be sufficient to change the vote of the Advisory Committee to approval." 58/

Following the "approvable" letter, Knoll submitted additional blood pressure analysis, agreed to withdraw the 20 mg dose, and revised the proposed labeling to advise that doses above 15 mg/day are not recommended. Cautionary statements regarding dosing were also incorporated into labeling within the WARNINGS and DOSAGE AND ADMINISTRATION Sections, and in the Patient Information Insert. The Division Director concluded, "Our analysis showed that limiting dosage to 15 mg will significantly decrease the number of patients who experience hypertension. This increase in safety will be accomplished with only a small loss in efficacy." 59/

As directed by the Division, Knoll also developed a Patient Information Insert for Meridia to enhance the safe and effective use of the drug. And as the Advisory Committee recommended, 60/ Knoll committed to the continued study of Meridia, which has been done.

The final FDA-approved Meridia product label incorporated numerous additions to enhance the safe and effective use of Meridia including, in part, the following information:

- **CLINICAL STUDIES** Section: a detailed analysis of patient responder information was added that helps identify patients

56/ See Letter from James Bilstad, Director, Office of Drug Evaluation, CDER, FDA, to Abraham Varghese, Knoll Pharmaceutical Company (Nov. 8, 1996) ("Approvable Letter").

57/ See Memorandum to the File from Solomon Sobel, Director Division Metabolic and Endocrine Drug Products, FDA, at 1 (Nov. 1, 1996).

58/ *Id.* at 2.

59/ See Memorandum to the File from Solomon Sobel, Director Division Metabolic and Endocrine Drug Products, FDA at 1 (Nov. 18, 1997).

60/ See Advisory Committee Transcript at 273-81.

most likely to achieve significant long-term weight loss with Meridia. Additionally, safety information describing mean blood pressure and heart rate changes seen with Meridia were added to this section.

- **WARNINGS** Section: information regarding blood pressure and heart rate increases coincident with Meridia use were added. Information regarding use in patients with a history of coronary artery disease, congestive heart failure, arrhythmias or stroke, as well as narrow angle glaucoma were included in the final product labeling. The need to assess blood pressure prior to therapy and at regular intervals during therapy was stated, including dose reduction or discontinuation considerations.
- **PRECAUTIONS** Section: information addressing use of Meridia in patients with seizures and various other disorders was included. Information regarding pulmonary hypertension was added.
- **DOSAGE AND ADMINISTRATION** Section: the proposed 20 mg dose was eliminated. This section also incorporated information on proper dose titration.

After final approval, the company continued to improve the labeling to support safe and effective use of Meridia, as reflected in additional labeling modifications:

- **CLINICAL TRIALS** Section: new information on the safe and effective use of Meridia for up to 2 years was added. Additional data on the blood pressure effects of Meridia were also added.
- **ADVERSE REACTIONS** Section: a new "Postmarketing Reports" Section was added which lists voluntary reports of adverse events temporally associated with the use of Meridia since the original approval. Although these events occurred during treatment with Meridia, they may have no causal relationship to the drug. Obesity itself, concurrent disease states, risk factors, or weight loss may be associated with an increased risk for some of the events.

These additions provide further information in support of the safe and effective use of Meridia.

As with any drug product, safety and effectiveness can be considered only in relation to the approved labeling. The 1997 product labeling reflected the

analysis of the Division as well as the comments from the Advisory Committee, and was part of the final FDA decision that Meridia is “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.” ^{61/} FDA did not, as HRG suggests, sweep aside the concerns raised in the medical review of Meridia. To the contrary, the Division used several different approaches to address these issues and carefully weighed the blood pressure effect against the substantial benefits that Meridia offers for the appropriate patient population.

B. The Petition Misrepresents the Efficacy of Meridia

HRG’s inherent bias is that Meridia is essentially “all risk and no benefit.” The facts prove otherwise.

The efficacy of Meridia is, foremost, based on three pivotal, placebo-controlled clinical trials (using a randomized, double-blind, placebo-controlled format) as presented in the original NDA. These three studies (BPI 852, SB 1047, and SB 1049) independently demonstrate that appropriate use of sibutramine results in significant weight loss compared to placebo. Further, in 2001, FDA and the sponsor added results from another randomized trial (SB 1048) to the approved labeling. SB 1048 confirms that sibutramine use can result in substantial weight loss as well as maintain the chance of weight loss for up to two years compared to placebo. Finally, two recently published studies, including more than 6,500 patients treated with sibutramine in general practice settings (KD 9618 and KD 9901), add decisively to the conclusion that appropriate use of Meridia helps patients achieve significant weight loss. These studies are summarized in the following table, based on the last observation carried forward analysis (LOCF) ^{62/}, and are discussed further below.

^{61/} 21 U.S.C. § 355(d)(1).

^{62/} A LOCF analysis captures data on all study patients. Therefore, it is more rigorous than other analyses.

**TABLE 1: EFFICACY RESULTS IN CLINICAL STUDIES
 (LOCF ANALYSIS)**

Study	No of patients at baseline	Design	Mean weight loss (lbs)			>5% weight loss		
			10 mg	15 mg	Placebo	10 mg	15 mg	Placebo
BPI852	1047	24-week, R, PC	-9.7*	-12.1*	-2.0	45%*	53%*	13%
SB1047	485	12-month, R, PC	-9.8*	-14.0*	-3.5	39%*	57%*	20%
SB1049 ^a	160	12-month, R, PC	-28.4*	-	-15.2	86%*	-	55%
SB1048	605	6-month open label, weight loss phase, 18-month, R,PC weight maintenance phase	-20.5*	-	-11.7	67%*	-	49%
KD9618 ^{bc}	606	48-week, R,PC	-	-17.4*	-8.4	-	65%*	35%
KD9901	6,630	12-week open label	-22.2 ^d	-	-	84% ^d	-	-

R: randomised; PC: placebo-controlled

a: Weight loss data shown describes changes in weight from the pre-VLCD weight; mean weight loss during the 4-week VLCD phase was 16.9 lbs in patients who subsequently received sibutramine and 16.3 lbs in patients who subsequently received placebo.

b: Data includes results from placebo and continuous dosing arms only

c: Number of patients at screening

d: Dose may be titrated to 15 mg at week 4

*p<0.05 compared to placebo

1. Pre-Market Studies

Study BPI 852 was a dose-ranging study (1 mg to 30 mg) of 6 months duration in 1,047 patients with a BMI of 30 to 40 who received counseling on calorie-reduced diet, exercise, and behavioral modification. ^{63/} Sibutramine-treated patients obtained a mean weight loss of 9.7 pounds on a 10 mg dose and 12.1 pounds on a 15 mg dose, compared to a mean weight loss of 2.0 pounds on placebo

^{63/} See G.A. Bray, *Sibutramine Produces Dose-Related Weight Loss*, 7 OBESITY RESEARCH 189, 190 (1999).

(LOCF). ^{64/} Significantly more sibutramine-treated patients achieved clinically important weight loss of greater than 5% of initial body weight (45% on 10 mg, and 53% on 15 mg, *versus* 13% on placebo).

Study SB 1047 was a primary care based study of 12 months duration in 485 patients with a BMI of 27 to 40 who were counseled on maintaining a calorie reduced diet. ^{65/} The mean weight loss in sibutramine treated patients was 9.8 pounds on a 10 mg dose and 14.0 pounds on a 15 mg dose, compared to only 3.5 pounds on placebo. ^{66/} Significantly more sibutramine-treated patients achieved weight loss greater than 5% of initial body weight (39% on 10 mg, and 57% on 15 mg, *versus* 20% on placebo). ^{67/}

Study 1049 was a specialist based study (obesity or endocrinology) of 12 months duration in 159 patients with a BMI greater than 30 who, for 4 weeks, were maintained on a very low calorie diet (VLCD) (220 to 800 kcal/day). ^{68/} Patients who lost at least 13.2 pounds after the VLCD phase were eligible for the 12 month double-blind treatment phase. ^{69/} These patients received sibutramine or placebo and were counseled on maintaining a calorie reduced diet (20% to 30% calorie reduction from their standard diet). Mean weight loss during the four-week VLCD phase was 16.9 pounds in patients who subsequently received sibutramine and 16.3 pounds in patients who subsequently received placebo. ^{70/} At the end of the treatment phase, the overall mean weight loss in sibutramine treated patients was 28.4 pounds on a 10 mg dose compared to only 15.2 pounds on placebo, from the pre-VLCD weight. ^{71/} Significantly more sibutramine-treated patients achieved weight loss of greater than 5% of initial body weight (86% on 10 mg *versus* 55% on placebo). ^{72/}

^{64/} See Meridia Labeling, Clinical Studies, tbl.

^{65/} I.G. Smith, *Randomized Placebo-Controlled Trial of Long-Term Treatment with Sibutramine in Mild to Moderate Obesity*, 50 J. FAMILY PRACTICE 505, 506-06 (2001).

^{66/} See Meridia Labeling, Clinical Studies, tbl.

^{67/} Smith at 509, tbl. 2.

^{68/} See M. Apfelbaum et al., *Long-Term Maintenance of Weight Loss After a Very-Low-Calorie Diet: A Randomized Blinded Trial of the Efficacy and Tolerability of Sibutramine*, 106 AM. J. MED. 179, 180 (1999).

^{69/} *Id.*

^{70/} *Id.* at 180, tbl. 1.

^{71/} See Meridia Labeling, Clinical Studies, tbl.

^{72/} Apfelbaum at 182.

FDA evaluated these results and concluded, as the Advisory Committee had done, that the studies met the agency's own recommended endpoint for weight-control products—a five percent reduction in initial body mass. ^{73/} The agency adopted that endpoint after analyzing the risks of obesity and concluding that “preventing obesity, and/or losing weight, might prevent or reverse at least some of [the] morbidities” associated with the disease, such as hypertension, cardiovascular disease, and stroke. ^{74/} Based on these factors, FDA concluded that Meridia promotes clinically meaningful weight loss compared to placebo when used in conjunction with a reduced calorie diet.

2. Post-Market Published Studies

On April 17, 2000, Knoll submitted to FDA the results of a two-year maintenance study of Meridia. The agency agreed that this data supported the continued use of Meridia and Knoll added the study results to the drug's labeling. The study (SB 1048), was a two year study of weight maintenance in 605 patients with a BMI of 30-45 who received a reduced calorie diet, exercise counseling, and behavioral modification. ^{75/} During the six month, open label phase, when all patients received 10 mg of sibutramine daily, 94% of patients achieved $\geq 5\%$ weight loss. The mean weight loss was 26 pounds. ^{76/} Patients who achieved $\geq 5\%$ weight loss during this phase were eligible to be randomized for an additional 18 months in the double-blind, placebo-controlled phase. ^{77/} During this phase, physicians had the option of increasing the dose of sibutramine or placebo to 15 mg if weight regain occurred, to a maximum dose of 20 mg if further weight increases occurred.

After two years of treatment, 69% of sibutramine treated patients (compared to 42% on placebo) maintained at least 5% weight reduction, while 46% of treated patients (compared to 20% on placebo) maintained at least 10% weight reduction. ^{78/} Also after two years, about 43% of the sibutramine treated patients maintained 80% or more of their original weight loss (*i.e.*, their weight loss at 6 months) compared to 16% on placebo. ^{79/} The mean weight loss from initial body

^{73/} See Guidance for the Clinical Evaluation of Weight-Control Drugs, Division of Metabolic and Endocrine Drug Products, FDA, at 5 (Sept. 24, 1996).

^{74/} *Id.* at 1.

^{75/} W.P.T. James et al., *Effect of Sibutramine on Weight Maintenance After Weight Loss: A Randomized Trial*, 356 LANCET 2119, 2120 (2000).

^{76/} *Id.* at 2120, tbl. 1.

^{77/} *Id.* at 2120.

^{78/} *Id.* at 2121, fig. 3.

^{79/} *Id.* at 2122.

weight to endpoint was 21 pounds for sibutramine patients and 12 pounds for placebo patients. 80/

This study confirmed that sibutramine promotes clinically significant weight loss and weight maintenance in a statistically significant population. FDA agreed and approved a labeling change in February 2001, adding a discussion of the study to the Meridia labeling.

Finally, the results of two recently published clinical studies confirm the effectiveness of Meridia in the treatment of obesity. Study KD 9618 was a post-approval randomized trial, performed primarily in private practice clinics, for 48 weeks in 1,001 patients with a BMI 30 to 40 who received dietary advice. 81/ Patients who achieved at least a 2% reduction in BMI and/or 4.4 pounds of weight loss during the four week open label phase, when treated with a 15 mg dose of sibutramine daily, were randomized to continuous or intermittent therapy with a 15 mg dose of sibutramine daily or placebo. 82/ Sibutramine-treated patients obtained a mean weight loss of 17.4 pounds compared to 8.4 pounds in patients on placebo. 83/ Significantly more sibutramine-treated patients achieved weight loss of greater than 5% of initial body weight (65% on a 15 mg dose *versus* 35% on placebo). 84/

Study KD 9901 was a 12 week postmarketing surveillance study performed in general practice conditions in Germany, in 6,360 patients with a BMI of >30 (or BMI > 27 in patients with co-morbidities). All patients in the study received advice about diet and increased physical activity and were treated with sibutramine using 10 or 15 mg doses daily. 85/ Patients had a mean weight loss of

80/ Meridia Labeling, Clinical Studies.

81/ A. Wirth and J. Krause, *Long-Term Weight Loss With Sibutramine*, 286 JAMA 1331, 1333 (2001).

82/ *Id.* at 1332. Because intermittent dosing of sibutramine is not approved in the U.S., data from that group is not discussed here.

83/ *Id.* at 1334.

84/ *Id.*

85/ J. Scholze, *Adipositaehandlung mit Sibutramine unter Praxisbedingungen: Positive Effekte auf Metabolische Parameter und Blutdruck*, 127 DEUTSCH MED. WOCHENSCHR 606 (2002) (a translation of this article is included in the cited references).

22.2 pounds. ^{86/} Overall, 84% of patients lost greater than 5% of initial body weight, 45% lost greater than 10% and 14% lost greater than 15%. ^{87/}

This data, now published in the peer-reviewed literature, demonstrate clinically significant weight loss with sibutramine. HRG would prefer otherwise, claiming that only long-term morbidity and mortality studies would be meaningful. Were that the standard, few drugs for chronic conditions such as obesity and hypertension would ever be approved. The point remains: Meridia has been proven to meet the FDA's guideline for efficacy for weight loss products and, in post-market studies, continues to meet or exceed the agency's mark.

C. The Petition Misrepresents the Safety of Meridia

HRG bases its assault on Meridia's safety record on two types of data—pre-approval clinical studies and post-market adverse event ("AE") data. ^{88/} According to HRG, placebo controlled trials showed a "significant increase in blood pressure, heart rate and abnormal electrocardiograms" and "blood pressure screening may therefore not prevent those at risk of sibutramine's dangerous increases in blood pressure from receiving the drug." ^{89/} In fact, HRG has misstated the clinical trial safety data to suggest concerns that simply have not been borne out on objective analysis.

1. Safety: Clinical Studies

Knoll's original submission to FDA included an integrated database that contained safety data collected in placebo-controlled clinical studies performed in patients with either obesity, depression, or in normal volunteers. The database, which was based on studies completed as of September 30, 1994, included 1,766 obese patients on sibutramine therapy and 605 obese patients on placebo. Knoll supplemented these data in February 1997 with additional placebo-controlled data. ^{90/} In all, this integrated database was taken from 64 clinical trials. The placebo-controlled studies included 3,201 sibutramine-treated patients of whom 2,068 patients were obese and 1,411 placebo-treated patients of whom 884 patients were obese.

^{86/} Scholze at 3 (translated version).

^{87/} Scholze at 3 (translated version).

^{88/} See generally HRG Citizen Petition.

^{89/} HRG Citizen Petition at 2.

^{90/} See Memorandum from Bruce V. Stadel, Medical Officer/Epidemiology, FDA to Eric Colman, Medical Officer/Metabolic-Endocrine Group 2, FDA, at 1 (Mar. 25, 1997).

As shown in Table 2 below, this database very clearly establishes that sibutramine does not predispose obese patients to the risks identified by HRG.

TABLE 2: NUMBER (%) OF OBESE PATIENTS WITH ADVERSE EVENTS IN PLACEBO-CONTROLLED STUDIES

COSTART preferred term	Placebo	Sibutramine
Cerebrovascular accident (stroke)	1/884 (0.1%)	2/2068 (0.1%)
Acute interstitial nephritis	884 (0%)	1/2068 (0.05%)
Thrombocytopenia	884 (0%)	0/2068 (0 %)
Bleeding disorders	1/884 (0.1%)	14/2068 (0.7%)
Palpitations	7/884 (0.8%)	41/2068 (2.0%)
Vasodilatation	8/884 (0.9%)	49/2068 (2.4%)

In addition, at FDA's request, 91/ Knoll amended the NDA to include an analysis of vital signs recorded during the clinical trials, to determine if sibutramine raised blood pressure or heart rate above rates seen in patients taking placebo. Based on its pharmacological action, treatment with sibutramine results in dose-related increases in blood pressure and heart rate. The approved doses were selected to minimize these effects. The results of the analysis are presented in Table 3, below.

91/ See Approvable Letter.

TABLE 3: META-ANALYSIS OF VITAL SIGN CHANGES FROM BASELINE BY TREATMENT GROUP AND 5% WEIGHT LOSS RESPONDERS

(LOCF ANALYSIS)

Treatment group	No of pts	SBP (mm Hg)	DBP (mm Hg)	Pulse rate (bpm)
All placebo [#]	219	+0.77	+0.77	-0.96
Sibutramine 5mg				
All	222	+1.86	+1.44	+2.87*
<5% wt loss	152	+2.11	+2.34	+3.29*
≥5% wt loss	70	+1.25	-0.50	+1.92*
All placebo [#]	515	-2.10	-1.43	-0.55
Sibutramine 10 mg				
All	527	-0.60	+0.26	+3.21*
<5% wt loss	280	+0.79	+1.32*	+2.97*
≥5% wt loss	247	-2.19	-0.93	+3.42*
All placebo [#]	405	-0.21	-0.22	+0.54
Sibutramine 15 mg				
All	416	+2.01*	+1.52*	+4.24*
<5% wt loss	209	+3.00*	+1.87*	+4.45*
≥5% wt loss	207	+0.99	+1.05	+3.91*

*p<0.05 compared to placebo

[#]comparative placebo group for designated sibutramine dose

These results demonstrate that the approved doses are associated with very small mean increases in blood pressure and heart rate for sibutramine-treated patients. Moreover, these mean changes are ameliorated when sibutramine-treated patient lose >5% of body weight. Most importantly, in clinical trials, these small mean changes did not result in clinically important cardiovascular consequences. Researchers did not see relevant differences in reports of myocardial infarction, myocardial ischemia, heart failure, cardiomyopathy or strokes between sibutramine-treated and placebo-treated patients. Similar results were noted in study SB1048, discussed above, which evaluated the use of sibutramine (10 to 20 mg) for up to 2 years compared to placebo. 92/

92/ See James at 2121, fig. 3.

Moreover, there was no material difference in the percentage of sibutramine-treated patients compared to placebo-treated patients who discontinued a study due to increased blood pressure (0.8 vs 0.3%), increased heart rate (0.3 vs 0.1%) or palpitations (0.3 vs 0%). “[I]n pre-marketing placebo-controlled obesity studies, 0.4% of patients treated with Meridia were discontinued for hypertension (SBP > 160 mm Hg or DBP > 95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients with Meridia were discontinued for tachycardia (pulse rate > 100 bpm), compared with 0.1% in the placebo group.” 93/

Nevertheless, as a precaution, Knoll agreed to include in the labeling for Meridia a bolded Warning statement: “Treatment with Meridia has been associated with increases in heart rate and/or blood pressure. Therefore, Meridia should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.” 94/ In addition, Knoll agreed to lower the maximum dose of sibutramine, based on the possibility of dose-related increases in blood pressure and heart rate. 95/

HRG claims that “blood pressure screening may . . . not prevent those at risk of sibutramine’s dangerous increases in blood pressure from receiving the drug.” 96/ However, the approved product labeling includes recommendations to help ensure proper patient use. The product label notes under the Warning Section that “blood pressure and pulse rate should be measured prior to starting therapy with Meridia and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving Meridia, either dose reduction or discontinuation should be considered. Meridia should be given with caution to those patients with a history of hypertension and should not be given to patients with uncontrolled or poorly controlled hypertension.” These recommendations were included to advise prescribers about appropriate patient use and monitoring.

93/ Meridia Labeling, Warnings.

94/ *Id.* at 6. The labeling for Meridia contains information from a 12-week, placebo-controlled study that evaluated sibutramine’s effects at 15 mg on blood pressure variability measured over 24-hour periods using ambulatory blood pressure monitoring. These data became available after the 1997 approval and confirm that although mean systolic and diastolic blood pressure readings were, as expected, generally higher on sibutramine than on placebo treatment, there was no change to the normal diurnal variations or expected nocturnal reduction.

95/ See Meridia Labeling, Dosage and Administration.

96/ HRG Citizen Petition at 2.

Finally, and contrary to HRG's claim, there were no differences in abnormal EKG reports or arrhythmias between sibutramine-treated and placebo-treated subjects in placebo-controlled clinical studies. This is demonstrated in Table 4, below.

TABLE 4: NUMBER (%) OF PATIENTS WITH CARDIAC DYSRHYTHMIAS AS ADVERSE EVENTS IN ALL PLACEBO-CONTROLLED STUDIES

COSTART Preferred term	Placebo N=1411 (n, %)	Sibutramine N=3201 (n, %)
Abnormal EKG	2 (0.1)	15 (0.5)
Arrhythmia	1 (0.1)	5 (0.2)
Atrial arrhythmia	1 (0.1)	0
Atrial fibrillation	0	1 (<0.1)
Supraventricular extrasystoles	1 (0.1)	3 (0.1)
Ventricular extrasystoles	3 (0.2)	11 (0.3)

In all, HRG's characterization of the pre-market data is simply wrong. The data do not reveal any risks or safety issues not appropriately characterized in the labeling.

2. Safety: Postmarketing

According to the Petition, the AE data for sibutramine is grave; so much so that Meridia, according to HRG, must be declared "an imminent hazard to public health." Once again, the data show otherwise.

The worldwide reporting rate of fatalities coincident with Meridia is well below that expected for obese patients, even considering the possibility of under-reporting in the post-marketing setting, and the reported fatalities generally reflect the co-morbid conditions and risk factors associated with obesity.

More specifically, adverse event information concerning fatal outcomes since the international birthdate (earliest worldwide approval and marketing) of Meridia through March 10, 2002 shows a rate of 2.13 reports per 100,000 patient years. In contrast, the all-cause fatality rate for women with a BMI between 29.0 and 31.9 was approximately 390 deaths per 100,000 patients in a 16-year follow-up study of over 115,000 women between the ages of 30-55 with no history of

cardiovascular disease or malignancy. ^{97/} Although post-approval adverse event reporting is likely to underestimate the true incidence, the reported fatality rate coincident with sibutramine is nearly 200-fold lower than that reported in the obese population in this study.

The causes of death that have been reported as coincident with the use of sibutramine are, by and large, heterogeneous. While a number of the reports described death secondary to cardiac events, most reports described either alternative etiologies or complicating conditions, reflecting the known comorbidities of obesity. As to the remaining cases, the information was insufficient to allow for a meaningful analysis. The cardiac events described were also variable, including ischemia, heart failure, and arrhythmias. These data are consistent with the recognized increased risk of cardiovascular death associated with increased obesity. ^{98/}

Patients who are eligible for treatment with Meridia are at substantial risk of death and other severe morbidities due to their underlying disease. The nature of the deaths reported coincident with sibutramine is consistent with the risk profile of the obese population. Additionally, the reported fatality rate as coincident with sibutramine is nearly 200-fold lower than that reported in the obese population. The body of evidence simply does not point to an increased risk of death associated with use of the drug.

V. CONCLUSION

Obesity has emerged as a major threat to personal, public, and economic health worldwide. Ironically, obesity is universally recognizable, yet it is not universally recognized as the serious medical condition that it is, despite its litany of health consequences, including premature death. In fact, approximately 300,000 deaths per year may be attributed to obesity in the United States. Meridia is one of only two approved drugs for obesity and long-term weight management. It thus serves an important medical need for many patients. Its approval was based on multiple randomized, controlled, clinical trials, which are the gold standard for the demonstration of safety and efficacy. Since Meridia was first approved in 1997, more than 8.5 million people have used it for the management of obesity.

^{97/} See J.E. Manson, et al., *Body-Weight and Mortality Among Women*, 333 NEW ENGL. J. MED. 677, 679, table 1 (1995).

^{98/} See *id.* at 681.

Against this backdrop of facts and data, HRG's petition is without merit. It does not objectively represent the safety, efficacy, or regulatory review process which led to the approval of Meridia. We have shown that the regulatory review of Meridia by the FDA was robust and scientifically-driven. The issues raised during the review process were thoroughly and responsibly addressed. We have shown that the efficacy of Meridia, in study after study, is of a magnitude and durability that is clinically important in the management of obesity. We have shown that the safety of Meridia is well-characterized and transparently represented in the product information, providing responsible guidance to both the appropriate use of Meridia as well as its potential risks. The HRG Petition is thus at odds with an overwhelming body of data. It is an idiosyncratic and unscientific opinion which does not factually support its call for the withdrawal or ban of Meridia. Moreover, to the extent that it has sounded a false alarm among patients and physicians who rely on Meridia to treat obesity, it is a disservice to public health.

We respectfully request the prompt and unqualified denial of the Petition and we appreciate your careful consideration of this matter.

Sincerely,

A handwritten signature in black ink, appearing to read 'Eugene Sun', written in a cursive style.

Eugene Sun, M.D.

Divisional Vice President, Global
Pharmaceutical Development

Abbott Laboratories

Secretary Tommy Thompson

April 26, 2002

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cc: FDA Docket Number 02P-0120/CP1
FDA Deputy Commissioner Lester M. Crawford