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October 20, 2003

Dockets Management Division
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments in Opposition to Supplemental Petition to Ban Meridia® (FDA Docket No. 02P-0120/Sup 1)

Dear Sir or Madam:

Abbott Laboratories ("Abbott") is writing to oppose the supplemental petition ("Supplemental Petition") submitted by Public Citizen Health Research Group ("HRG") on September 3, 2003, to the above-referenced docket.

In March 2002, HRG petitioned Secretary Tommy Thompson to declare Meridia® (sibutramine hydrochloride monohydrate) "an imminent hazard to public health." 1/ Abbott promptly submitted extensive comments in opposition to the petition, demonstrating that HRG failed as a matter of law and science to justify its extraordinary request for relief. 2/ Eighteen months have passed since the Original Petition, and HRG's allegations remain baseless. In fact, since then and as discussed below, two major regulatory bodies have reconfirmed the safety and efficacy of Meridia®, and the product appropriately remains approved in over 70 countries as a safe and effective treatment for obese patients in need of long-term weight management.

02P-0120 C 4

1/ Petition of Public Citizen Health Research Group to Tommy Thompson, Department of Health and Human Services (Mar. 19, 2002) (FDA Docket No. 02P-0120/CP1) ("Original Petition").

2/ Comments of Abbott Laboratories to Tommy Thompson, Department of Health and Human Services (Apr. 26, 2002) (FDA Docket No. 02P-0120/C1) ("Abbott Opposition").

Now, in an attempt to revive its Original Petition, HRG has come forward with what it claims to be supplemental information, a "new analysis," and yet another reason why Meridia® should be "banned."[3/] As shown below, however, HRG's Supplemental Petition presents no new facts or issues that warrant any changes in the approval of Meridia®.

In addition to the fact that HRG's latest Supplemental Petition is as unfounded and misleading as its first, Abbott is concerned that HRG, along with mass tort lawyers, is using the Food and Drug Administration's ("FDA's") citizen petition process to fuel ongoing product liability suits concerning Meridia®. [4/] Two days after submitting its Supplemental Petition to FDA, HRG (not a party to any litigation involving Meridia®) wrote to the Honorable James Gwin, who is presiding over the Meridia® multi-district litigation ("MDL"), asking for broad disclosure of certain confidential information about Meridia®.[5/] At the same time, the HRG's petitions were submitted to Judge Gwin by the MDL plaintiffs. The timing of these actions is no coincidence. Lacking factual and scientific support for their claims, the MDL plaintiffs' case is flagging, and they are now using HRG and FDA's citizen petition process in an attempt to sustain their position in the litigation. Likewise, any progress made in the MDL by plaintiffs benefits HRG by advancing that organization's anti-Meridia agenda, regardless of the merits of HRG's arguments before the FDA.

HRG's Original and Supplemental Petitions continue to generate unwarranted uncertainty regarding the safety, efficacy, and regulatory status of sibutramine. Accordingly, we respectfully request that the agency act quickly to officially deny HRG's petitions and take the opportunity to affirm the safety and effectiveness of Meridia®. By taking such action, FDA will best serve the interests of patients afflicted with obesity, who stand to benefit from this safe and effective drug.

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3 Supplemental Petition of Public Citizen Health Research Group to Mark B. McClellan, Food and Drug Administration (Sept. 3, 2003) (FDA Docket No. 02P-0120/SUP 1) ("Supplemental Petition").

4/ Meridia® is currently the subject of multi-district litigation entitled *In re Meridia® Products Litigation*, No. 1481, pending in the U.S. District Court for the Southern District of Ohio.

5/ *See* Exhibit A attached. Abbott also attaches copies of referenced sources that are not readily available in alphabetical order. *See* 21 CFR 10.20(c)(iv).

I. HRG'S SUPPLEMENT RAISES NO NEW ISSUES OF CONCERN

The Supplemental Petition focuses on the same cardiovascular risks addressed in the Original Petition that Abbott comprehensively refuted in Abbott's initial Opposition almost 18 months ago. HRG makes no attempt in the Supplemental Petition to answer Abbott's original analysis; HRG simply repeats the same baseless arguments and theories it raised the first time.

HRG also attempts to raise what it characterizes as a "new and worrisome" concern: fetal toxicity. [6/] Not surprisingly, however, HRG fails to produce any convincing data to support this new assertion. HRG ignores the critical science regarding the prevalence of birth defects generally, and the documented association between obesity and an increase in negative pregnancy outcomes. HRG, as is its pattern, also completely misrepresents the thorough FDA approval process during which the agency comprehensively assessed potential risks to the fetus. In sum, HRG has failed to present any new issue that FDA has not already considered – let alone an issue that would warrant withdrawal of approval.

A. Cardiovascular Risks

The Supplemental Petition reiterates the contention that Meridia® poses unacceptable cardiovascular risks and, relying on a claim that "30 more cardiovascular deaths [have been] reported in the latest 18-month period," further asserts that there is a "rising number" of cardiovascular event reports associated with Meridia®. [7/] These assertions are deceptive.

As Abbott has previously demonstrated, results from controlled clinical trials do not show any meaningful differences in cardiovascular events between sibutramine-treated and placebo-treated patients. [8/] Likewise, HRG's reliance on an absolute number of adverse event reports is misguided because the significance of this figure can only be determined by considering the overall use of sibutramine in the general population. When such overall use factors are correctly considered, no adverse conclusions can be drawn from the data. Moreover, any increase in the number of reports coincident with the

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6/ Supplemental Petition at 2.

7/ *Id.* at 1-2.

8/ Abbott Opposition at 23.

use of Meridia® seen since HRG filed its Original Petition is neither surprising nor unexpected. Numerous factors unrelated to the effects of a drug influence the number of adverse drug experience reports received by a manufacturer. [9/] For example, HRG's Original Petition itself led to publicity, which is a well-documented cause of increased levels of adverse event reporting. [10/]

HRG also inaccurately reports that, since the filing of HRG's Original Petition, the cause of death in most patients taking Meridia® are heart attacks and cardiac arrests, and that there is a causal connection between the drug and fatalities allegedly reported in patients who have taken Meridia®. [11/] As noted above, however, any analysis of aggregate adverse event data must consider the expected background incidence of the reported events in the general population of obese persons. As demonstrated in the Abbott Opposition, the worldwide reporting rate of fatalities coincident with sibutramine is well below the background incidence rates of fatalities in the general obese population. [12/] Indeed, the worldwide all-cause fatality reporting rate coincident with the use of Meridia® (Nov. 12, 1997 – April 2003) is 4.4 reports per 100,000 person years. By comparison, the all-cause fatality incidence rate for women with a BMI between 29.0 kg/m^2 and 31.9 kg/m^2, and no history of cardiovascular disease, has been reported at approximately 390 reports per 100,000 person years. [13/] For men with a BMI $\geq$ 30 kg/m^2 and no history of cardiovascular disease or malignancy, the all-cause fatality incidence rate has been reported between 1,530-2,110 per 100,000 person years. [14/]

9/ *See, e.g.,* M.L. De Bruin et al., *Non-Sedating Antihistamine Drugs and Cardiac Arrhythmias – Biased Risk Estimates from Spontaneous Reporting Systems?*, 53 BRITISH J. CLIN. PHARMACOL. 370 (2002) ("De Bruin et al."); C. Baum et al., *The Spontaneous Reporting System in the United States*, in PHARMACOEPIDEMOLOGY 131-132 (B.L. Strom ed., 2d ed. 1994) ("Baum et al."); J.C.P. Weber, *Epidemiology of Adverse Reactions to Nonsteroidal Anti-inflammatory Drugs*, 6 ADVANCES IN INFLAMMATION RESEARCH 1 (1984).

10/ De Bruin et al., *supra* note 9, at 371, 373; *see also* Baum et al., *supra* note 9, at 132.

11/ Supplemental Petition at 1-2.

12/ Abbott Opposition at 25.

13/ *Id.* at 25-26.

14/ A.G. Shaper et al., *Body Weight: Implications for the Prevention of Coronary Heart Disease, Stroke, and Diabetes Mellitus in a Cohort Study of Middle Aged Men*, 314 BRITISH MED. J. 1311 (1997); A. Rosengren et al., *Body Weight and Weight Gain During Adult Life in Men in Relation to Coronary Heart Disease and Mortality: A Prospective Population Study*, 20 EUR. HEART J. 269, 271 (1999).

HRG's additional claim that "Meridia commonly causes large, sustained increases in blood pressure . . ." is incorrect. [15]/ HRG presents no data to support this claim. As discussed in depth in the Abbott Opposition, approved doses of the drug are associated with small mean increases in blood pressure. [16]/ Moreover, these mean changes are ameliorated when sibutramine-treated patients lose more than 5% of bodyweight. [17]/ Most important, in clinical trials, these small mean changes did not result in clinically important cardiovascular consequences. [18]/

In short, HRG has ignored the critical factors relevant to any conclusions regarding cardiovascular risks presented by sibutramine. The Abbott Opposition to the HRG Original Petition discusses these factors in detail – something HRG chooses to ignore.

B. Fetal Abnormalities

In a transparent attempt to re-ignite negative publicity about Meridia® and fuel third-party tort litigation, HRG sounds false alarms concerning "fetal toxicity" allegedly caused by sibutramine. [19]/ Here again, HRG's claim is without merit because the data do not support HRG's hypothesis that Meridia® has caused fetal adverse events. Moreover, HRG ignores the incidence of birth defects in the general population, and the increased risk of negative pregnancy outcomes in the obese. FDA and Abbott have already considered these risks and included pregnancy warnings in the labeling, including recommendations that women taking Meridia® use contraception. Consequently, HRG raises no new issue warranting additional FDA action.

15/ Supplemental Petition at 1.

16/ Abbott Opposition at 23.

17/ *Id.*

18/ *Id.*

19/ It is noteworthy that among HRG's "adverse events" are several reports of "unintended pregnancy." Supplemental Petition, Appendix, Table 3. HRG provides no explanation of how these events are related to Meridia. Nor does HRG make any attempt to separate out from its "analysis" duplicate adverse events, for example, fetal anomalies leading to spontaneous abortions. Thus, it is not clear exactly how many adverse events HRG is complaining about.

1. The Data do not Support the Conclusion that Sibutramine Causes Fetal Adverse Events

HRG omits in its Supplemental Petition two critical facts concerning fetal toxicity: (1) birth defects and fetal death are not uncommon in the general population; and (2) obesity itself presents increased risks to the fetus. As discussed below, an analysis of sibutramine adverse event data that recognizes these facts reveals no risks to fetuses coincident with sibutramine use that do not also appear in the general obese and non-obese populations.

It is a sad fact that every three and a half minutes a baby is born with a birth defect. [20]/ Congenital abnormalities of the heart and circulatory system affect more infants born than any other type of birth defect. [21]/ Birth defects account for 20% of all infant deaths, and the cause of 70% of all birth defects are unknown. [22]/ Several studies have demonstrated that the relative risk of neural tube defects in the offspring of obese women is increased twofold compared to the general population. [23]/ More recent data further supports the finding of a link between other birth defects and maternal obesity. In a study from the Center for Disease Control and Prevention ("CDC") examining the relative risk of birth defects in the overweight and obese population, obese women (BMI > 30 kg/m^2) had a two-fold or greater increased risk of offspring with heart defects, multiple anomalies, omphalocele and spina bifida when compared to the average-weight population. [24]/ Similarly, overweight women (BMI 25 – 29.9 kg/m^2) were found to have an increased risk of offspring with

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[20]/ March of Dimes Perinatal Data Companion, prepared by March of Dimes Perinatal Data Center (2002), *available at* http://www.marchofdimes.com/files/data_card.pdf.

[21]/ March of Dimes Perinatal Data Center, National Perinatal Statistics: Leading Causes of Birth Defects (2000) *available at* http://www.marchofdimes.com/printableArticles/680_2164.asp; *see also* R. Boneva et al., *Nausea of Pregnancy, Antinausea Preparations and Congenital Heart Defects: A Population-Based Control Study,* 149 AM. J. EPIDIMIOL. 717, 717 (1999).

[22]/ HHS, Centers for Disease Control, National Center on Birth Defects and Developmental Disabilities, *Report on the Metropolitan Atlanta Congenital Defects Program* (2002) at 3 ("MACDP Report").

[23]/ G. M. Shaw et al., *Risk of Neural Tube Defect-Affected Pregnancies Among Obese Women,* 275 JAMA 1093-1096 (1996); D. K. Waller et al., *Are Obese Women at Higher Risk for Producing Malformed Offspring?,* 170 AM. J. OBSTET. GYNECOL. 541, 544 (1994); M. L. Watkins et al., *Is Maternal Obesity a Risk Factor for Anencephaly and Spina Bifida?,* 7 EPIDEMIOLOGY 507, 511 (1996) ("Watkins et al. (1996)").

[24]/ M. L. Watkins et al., *Maternal Obesity and Risk for Birth Defects,* 111 PEDIATRICS 1152-57 (2003) ("Watkins et al. (2003)")(analyzing data from the CDC's Metropolitan Atlanta Congenital Defects Program and the Atlanta Birth Defects Risk Factor Surveillance Study).

heart defects and multiple anomalies when compared to the average-weight population. [25]/

Abbott, in fulfillment of its regulatory responsibilities, investigates and assesses adverse event reports, and submits regular reports to FDA. Sibutramine adverse event information concerning congenital anomalies received by the sponsor has been analyzed and presented to the agency. The pattern of anomalies reported coincident with sibutramine therapy is consistent with that expected in the general and obese populations. In addition, given that the overall rate of serious birth defects in live births in the general population is 3-4%, [26]/ and the rate of these events in the obese population is increased, analysis of these reports does not suggest a causal relationship between sibutramine and the observed events.

Furthermore, the CDC reports that 16% of all clinically recognized pregnancies end in spontaneous miscarriage and stillbirth, with the vast majority occurring early in pregnancy. [27]/ More than a third of all fetal and infant deaths, and greater than 50% of all prenatal deaths in Europe and North America are stillbirths. [28]/ Although in clinical practice the cause of spontaneous abortion is not usually known, [29]/ it is well recognized that a major cause of early pregnancy loss is chromosomal abnormality. [30]/ Additional risks of miscarriage and stillbirth include high maternal age (from late 30s), overt hypothyroidism or hyperthyroidism, poorly controlled diabetes,

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[25]/ Watkins et al. (2003), *supra* note 24, at 1154; Waller et al., *supra* note 23, at 544-45.

[26]/ *See* Centers for Disease Control and Prevention, "Program Brief: Centers for Birth Defects Research and Prevention" (Feb. 2003) *available at* http://www.cdc.gov/programs/defects2.pdf .

[27]/ S. Ventura et al., *Trends in Pregnancies and Pregnancy Rates by Outcome: Estimates for the United States, 1976-1996, in* HHS, CDC, National Center for Health Statistics, Vital and Health Statistics (Jan. 2000) at 1, 5 (citing data from 1996).

[28]/ O. Stephansson et al., *Maternal Weight, Pregnancy Weight Gain, and the Risk of Antepartum Stillbirth*, 184 AM. J. OBESTET. GYNECOL. 463, 463 (2001) ("Stephansson et al.").

[29]/ S. H. Eisinger, *Early Pregnancy Bleeding: A Rational Approach*, 3 CLINICS IN FAMILY PRACTICE 225, 230 (June 2001).

[30]/ J. L. Simpson, *Fetal Wastage, in* OBSTETRICS: NORMAL AND PROBLEM PREGNANCIES 731 (Steven G. Gabbe et al. eds., 4th ed. 2002); A. Garcia-Enguidanos et al., *Risk Factors in Miscarriage: A Review*, 102 EUR. J. OBSTET. GYNECOL. REPROD. BIO. 111, 113 (2002); R. O'Rahilly & F. Muller, *Stages, Age, Measurements, Growth and External Form Including the Face, in* HUMAN EMBRYOLOGY & TERATOLOGY 93 (3rd ed. 2001); W. J. Larsen, *Gametogenesis, Fertilization, and the First Week, in* HUMAN EMBRYOLOGY 22 (2d ed. 1997); M. Daniely et al., *Detection of Chromosomal Aberration in Fetuses Arising from Recurrent Spontaneous Abortion by Comparative Genomic Hybridization*, 13 HUMAN REPRODUCTION 805, 805 (1998).

obesity, and, in some studies, smoking. [31]/ Obesity also increases the risk of sudden intrauterine unexplained death with greatest risk in mothers having BMI > 30kg/m^2. [32]/

The timing of the spontaneous abortions analyzed and presented by Abbott to the agency is consistent with that reported in the literature as occurring in the female population. Obese and overweight women may be at increased risk for spontaneous abortions, congenital anomalies and stillbirths. The evidence does not establish a link between women who have taken sibutramine and miscarriage. Furthermore, Abbott's review of the single report of a stillbirth coincident with sibutramine use found that the event was not related to sibutramine.

2. FDA Has Reviewed Fetal Toxicology Information in Detail and Included Adequate Warnings in the Meridia Labeling

HRG's Supplemental Petition also misrepresents FDA's thorough review of sibutramine's potential risks to pregnant women and fetuses. In fact, FDA records reveal that agency professionals reviewed at least ten reproductive studies before approving the drug. [33]/ HRG focuses on selected statements from only four of these reports to support its unfounded attempt to raise yet another claim concerning the drug's safety. [34]/ Yet even these studies are misrepresented in HRG's Supplemental Petition.

For example, HRG cites one rabbit study where stenosis or atresia of the pulmonary trunk or valve was observed. Nowhere does HRG acknowledge that cardiac anomalies were seen in only five out of 415 rabbit

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[31]/ A. M. Andersen et al., *Maternal Age and Fetal Loss: Population Based Register Linkage Study*, 320 BRITISH MED. J. 1708-1712 (2000); L. L. Simpson, *Maternal Medical Disease: Risk of Antepartum Fetal Death*, 26 SEMINARS IN PERINATOLOGY 42-50 (2002); O. Langer, *A Spectrum of Glucose Thresholds May Effectively Prevent Complications in the Pregnant Diabetic Patient*, 26 SEMINARS IN PERINATOLOGY 196-205 (2002); S. Cnattingius & M. Lambe, *Trends in Smoking and Overweight During Pregnancy: Prevalence, Risks of Pregnancy Complications, and Adverse Pregnancy Outcomes*, 26 SEMINARS IN PERINATOLOGY 286-295 (2002).

[32]/ F. Froen et al., *Risk Factors for Sudden Intrauterine Unexplained Death: Epidemiologic Characteristics of Singleton Cases in Oslo, Norway, 1986-1995*,184 AM. J. OBSTET. GYNECOL. 694, 699 (2001); *see also* Stephansson et al., *supra* note 28, at 465-66.

[33]/ *See* FDA Summary Basis of Approval, Pharmacology Review, David Hertig, (Oct. 3, 1996) ("FDA Pharmacology Review").

[34]/ Supplemental Petition at 3.

fetuses – an incidence rate of 1.2 percent that is similar to the background rate for the strain of rabbits used in the study. [35]/ Nor does HRG disclose FDA's conclusion with respect to this and another teratology study that "[t]here appeared to be no specific teratology (birth defects) and the incidence of varied anomalies was not consistent among the different studies." [36]/ Likewise, with respect to one rat study, HRG states that certain cardiac anomalies (stenosis or septal defects) were seen in three pups of treated rats, but HRG ignores the FDA reviewer's note that the majority of the offspring of the treated rats were normal. [37]/

This selective use of the record highlights HRG's practice of taking out of context FDA statements from the vast sibutramine record of approval, and using them to misrepresent Meridia's safety profile. HRG simply ignores FDA's ultimate conclusion that the drug is safe and effective for its intended use. These critical and intentional omissions call into question the accuracy and completeness of HRG's submissions. *See* 21 C.F.R. § 10.30(b).

FDA has published regulatory guidance governing evaluation of animal reproductive and developmental toxicity data for potential human developmental and reproductive risks. [38]/ For reproductive toxicity, fertility, parturition, and lactation should be assessed. [39]/ For developmental toxicity, the relevant areas of inquiry are mortality, dysmorphogenesis (structural alterations), alterations to growth, and functional toxicities. [40]/ The reproductive studies conducted by Knoll were evaluated by FDA, the

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[35]/ FDA Pharmacology Review at 31, 65.

[36]/ *Id.* at 65

[37]/ *Id.* at 34. All three of the treated pups exhibiting a defect came from the lower dosed groups. *Id.*

[38]/ FDA, CDER, *Draft Reviewer Guidance: Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities* (Oct. 2001).

[39]/ *Id.* at 3.

[40]/ *Id.* at 3-4.

toxicology reviewer addressed all these areas,[41] and subsequently recommended approval. [42]

Finally, completely ignoring the reproductive studies conducted by Knoll and evaluated by FDA, HRG asserts that "fetal harm is not mentioned in the label." [43] This parsing of words is, at best, misleading. As HRG well knows, FDA has approved Meridia® as a safe and effective drug with the following statements in the approved labeling:

> For professionals: "The use of MERIDIA during pregnancy is not recommended. Women of childbearing potential should employ adequate contraception while taking MERIDIA. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy." [44]
>
> For patients: "MERIDIA should not be used by pregnant women or nursing mothers. You should notify your doctor immediately if you become pregnant or plan to become pregnant. [45] Women of childbearing potential should use an effective birth control while taking MERIDIA. Check with your doctor to make sure you are on a medically safe and effective birth control method while taking MERIDIA." [46]

These quotes from the approved labeling accurately reflect FDA's careful review of the relevant fetal toxicity data, another fact that HRG simply chooses to ignore.

41/ For example, FDA reviewed a rat fertility study, FDA Pharmacology Review at 21-22; perinatal and lactation studies in rats, *id.* at 32-36; and several teratogenicity studies performed in rats and in rabbits. *Id.* at 23-32. In general, these reproductive studies observed multiple parameters, such as parturition, offspring mortality, fetal structural alterations, fetal growth and body weight, and indices of functional toxicity. *Id.* at 21-36.

42/ FDA Pharmacology Review at 21-36; 66-67 (noting that Knoll carried out a "considerable number" of toxicity studies).

43/ Supplemental Petition at 3.

44/ Meridia Labeling, *Precautions, Pregnancy.*

45/ Meridia Patient Information, *"What if I am pregnant or nursing?"*

46/ Meridia Patient Information, *"What about sexual activity and potential pregnancy?"*

II. HRG FAILS TO ACKNOWLEDGE THE FINDINGS OF EUROPEAN AND CANADIAN REGULATORS

Not only has HRG, as discussed above, conveniently omitted key facts relating to the FDA's approval of Meridia®, it also has ignored subsequent decisions confirming the safety and efficacy of the drug reached by other regulatory bodies, worldwide.

Since its first approval in 1997, sibutramine has been approved in over 70 countries, including the 15 Member States of the European Union ("EU"). The first EU marketing authorization was granted in Germany in January 1999 following a comprehensive assessment of the drug. And, since then, the European Union's Committee for Proprietary Medicinal Products ("CPMP"), has issued two favorable opinions regarding the safety of sibutramine, after paying particular attention to the issue of cardiovascular risk. In November 2000, the CPMP reviewed the safety and efficacy of sibutramine and adopted a favorable opinion recommending maintenance of the German marketing authorization. This opinion grew out of concerns raised by Belgium during a Mutual Recognition Procedure, "that sibutramine gave rise to increased blood pressure and heart rate in a substantial number of users and that the long-term consequences of these effects were not sufficiently documented . . . ." [47] On the basis of the CPMP opinion, the remaining EU Member States granted national authorizations for sibutramine. The CPMP opinion was converted into a decision by the European Commission in March 2001.

In June 2002, the CPMP again issued a favorable opinion to maintain the marketing authorization for sibutramine. [48] This CPMP review was prompted by a request from the Italian Ministry of Health in response to certain Italian reports of adverse events, including two fatalities. The CPMP's assessment included a review of reports of fatalities coincident with the use of sibutramine. The analysis concluded that:

- There is substantial heterogeneity in the causes of death;

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[47] CPMP, *Opinion Pursuant to Article 12 of Council Directive 75/319/EEC as amended, for Sibutramine*, No. CPMP/2741/2000-EN, EMEA/H/A/A-12/349 (Nov 16, 2000) at 4.

[48] CPMP, *Opinion Following an Article 31 Referral: Sibutramine, No.* CPMP/4514/02/Final (Dec. 2, 2002) at 1, *available at* http://www.emea.eu.int/pdfs/human/referral/451402en.pdf.

- In most cases, alternative etiologies and complicating conditions, reflecting the known comorbidities of obesity, are present; and

- In the remaining cases, there is insufficient information to identify a cause of death. [49]/

In its report, the CPMP identified no new cardiovascular safety concerns and considered adequate the current statements relating to cardiovascular risk information in the approved product labeling. [50]/ The CPMP concluded that the benefit/risk balance of sibutramine remained favorable. [51]/ Given the CPMP's favorable opinion, in August 2002, Italy lifted its previously imposed marketing suspension on sibutramine. The CPMP opinion was converted into a decision by the European Commission in October 2002.

In December 2000, sibutramine was approved for marketing in Canada. After approval, Health Canada also conducted a safety review of sibutramine, prompted by the then-ongoing assessment by the CPMP. This inquiry resulted in Health Canada's conclusion in 2003 that sibutramine "continues to meet the requirements for sale in Canada." [52]/ Health Canada required no additional risk management measures or other safety actions for sibutramine.

HRG would have FDA and the public believe either that none of these worldwide safety reviews of sibutramine has occurred, or that the conclusions reached by each of these regulatory authorities are wrong. HRG's position– unsupported by any scientific analysis much less a rigorous one – can not trump the collective judgments of FDA, the CPMP, and the Canadian regulatory authorities, all of whom have judged sibutramine a safe and effective drug for the treatment of obesity.

49/ *Id.* at 18.

50/ *Id.* at 21.

51/ *Id.*

52/ Health Canada Advisory, *Health Canada Reports Back to Public on Safety Profile of Meridia® (sibutramine)* (Feb. 28, 2003), *available at* http://www.hc-sc.gc.ca/english/protection/warnings/2003/2003_07.htm.

III. HRG'S REAL AGENDA

HRG's real agenda is clear. Regardless of the fate of its petition before FDA, HRG can still advance its anti-Meridia agenda by collaborating with the mass tort lawyers in their legal assault against the drug. As detailed in the Abbott Opposition, HRG in its Original Petition inaccurately and misleadingly describes the lengthy approval process for Meridia®, and the safety of the drug. Some 18 months later, 15 months after the CPMP's second review of the drug's risk/benefit profile, and eight months after Canada reaffirmed the safety of sibutramine, HRG files its supplement, equally misleading and as baseless as its first petition. Immediately thereafter, plaintiffs in the tort litigation submit HRG's submissions to the MDL court. Then, HRG takes the unprecedented step of sending a letter to the judge presiding over the Meridia MDL litigation requesting certain information.

The agency should not permit the use of a pending citizen petition for the benefit of tort litigants. FDA can, and should, stop this abuse by quickly affirming its well-supported approval of Meridia as a safe and effective drug. It is incumbent on FDA to deny the HRG petitions based on both the evidence contained in Abbott's submissions to this docket and the comprehensive clinical data available to the agency. Should the docket remain open, HRG will simply use it to create additional opportunities to assist plaintiffs' lawyers to pursue claims against Meridia®. Of course, any progress made in the MDL by plaintiffs advances HRG's objective to remove Meridia from the marketplace, regardless of the merits of its arguments before FDA.

Unfortunately, left unanswered, HRG's petitions also create uncertainty for patients and their physicians. As our Original Opposition established, and as FDA has repeatedly acknowledged, obesity is a real and growing public health crisis. [53] Many patients who could benefit from weight loss may have been discouraged from trying pharmacotherapy in the face of HRG's actions. This situation should not be allowed to continue. FDA should act quickly to set the record straight -- Meridia is safe and effective as labeled.

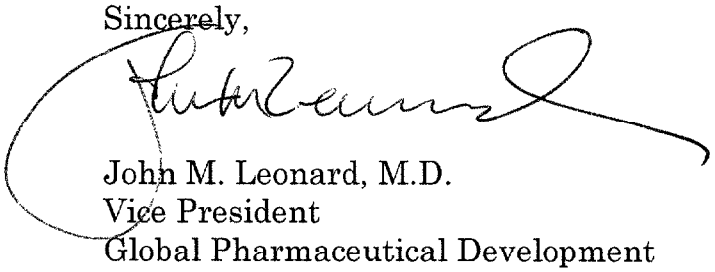
53/ Abbott Opposition at 4-8. Most recently, in an effort to combat the increasing obesity problem in the United States, FDA has scheduled for October 23, 2003, a public meeting to discuss, among other topics, medical intervention as a weight-loss treatment option. http://www.fda.gov/oc/opacom/hottopics/obesity.html.

IV. CONCLUSION

In what has become a pattern of irresponsible conduct, HRG's Supplemental Petition contains unfounded claims and misstatements of fact, omits pertinent information regarding Meridia's® safety and efficacy, and seeks to mischaracterize the data surrounding the drug. Adopting this strategy, HRG makes a thinly veiled attempt to keep the petition docket open, and cast a cloud over Meridia®.

FDA should put a stop to HRG's unsupported assault on Meridia by closing this proceeding with an official denial of HRG's Original and Supplemental Petitions, and a clear and concise statement that Meridia® is safe and effective when used as labeled for the treatment of obesity.

Sincerely,



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cc: HHS Secretary Tommy G. Thompson
FDA Commissioner Mark B. McClellan