DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 4 2001

Mark P. McGrath, Esq.
395 School Street
Watertown, MA 02472

Re: Docket No. 99P-4053/PRC1

Dear Mr. McGrath:

This letter responds to your petition for reconsideration dated October 6, 2000, submitted on behalf of Drs. Timothy Maher and Richard Wurtman regarding the proposed amendment to classification and product labeling for the sympathomimetic amine, phentermine.

You request reconsideration of the Food and Drug Administration's (FDA's) September 7, 2000, decision to deny your client's original citizen petition (99P-4053/CP-1). The original petition pertained to the labeling for phentermine and requested that the product labeling and patient insert for phentermine in all of its salt forms indicate that it inhibits the enzyme monoamine oxidase, classifying it as a monoamine oxidase inhibitor. You also request that the current language of the approved labeling and patient insert be modified to state that phentermine is capable of inhibiting monoamine oxidase (MAO) and therefore should not be used concurrently with sympathomimetic amines or selective serotonin reuptake inhibitors (SSRIs).

The Commissioner may grant a petition for reconsideration if the Commissioner determines the petition to be in the public interest and in the interest of justice. The Commissioner will grant a petition for reconsideration if the Commissioner determines all of the following apply:

(1) The petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered.
(2) The petitioner's position is not frivolous and is pursued in good faith.
(3) The petitioner has demonstrated sound public policy grounds supporting reconsideration.
(4) Reconsideration is not outweighed by public health or other public interests.

21 CFR 10.33(d). For the reasons discussed below, FDA upholds its previous decision to deny the citizen petition.

I. Grounds for Reconsideration

You request reconsideration of your clients' original petition because you claim that the decision to deny it was based on inaccurate scientific data. You claim that the relevant information and views contained in the supporting documentation of the original citizen petition show sufficient justification to grant your clients' request for reconsideration of the citizen petition.

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II. Discussion

Your grounds for reconsideration of your clients' original citizen petition are listed below. FDA's response follows each of your statements.

1. FDA's letter denying the petition states on page 3 that the accepted manuscript from the *Journal of Biochemical Pharmacology* was not submitted for review. You claim that *Biochemical Pharmacology's* letter to Dr. Richard J. Wurtman informing him that his paper had been accepted for publication and the article itself were in the original citizen petition.

We acknowledge that in the original citizen petition, a copy of a manuscript entitled "Characterization of phentermine and related compounds as monoamine oxidase inhibitors (MAOI)" was provided. But we did not know whether the submitted manuscript was the published version or the revised for publication version. We did not receive a copy of the published article (or final accepted manuscript). The acceptance letter from Dr. Robert H. Roth, Associate Editor of *Biochemical Pharmacology,* was included in the reconsideration package. Dr. Roth's letter stated that Dr. Wurtman's ". . . revised manuscript . . . is now acceptable for publication . . . ," which implies that revision of the originally submitted manuscript was required for acceptance.

We obtained a copy of the published article (Ulus et al., *Biochem Pharmacol* 59(12): 1611-1621, 1999). Many revisions were made to the manuscript submitted in the original citizen petition. Although some were minor changes, we found a number of changes to data and text when the submitted manuscript was compared with the published article. For example, data for moclobemide were added to Table 1 and were removed from Table 2, data for phentermine were revised in Table 1, and data for tranylcypromine and phenelzine were revised in Table 2. In addition, the manuscript submitted in your clients' original petition did not have any of the figures included in the publication. Also, a note added in the proof of the published article was not included in the copy of the manuscript. According to this note, an acute oral dose of phentermine (15 milligrams (mg)) ". . . significantly increased platelet serotonin levels after 2 hours . . ." in 27 other women. No data were provided in the published report to support this statement.

2. You state that the proper way to express inhibition by a reversible MAOI is by the K_i value and that the proper way to express inhibition by an irreversible inhibitor is by the EC_{50}. Although one cannot make a direct comparison between the two measurements because the mechanisms of action are different, both values represent the value at which 50 percent of the enzyme is inhibited. Also, the value for moclobemide is similar enough to that of phentermine to make a meaningful comparison.

   You also claim that in its letter denying the citizen petition FDA states that a comparison between K_i and EC_{50} cannot be made. However, later in the letter the

concentration differences noted for phentermine and the irreversible agents mentioned (clorgyline, tranylcypromine) are "markedly higher," clearly indicating a comparison.

Enzyme inhibition is commonly expressed as IC_{50} or K_i. IC_{50} is the concentration of an inhibitor resulting in a 50 percent decrease in enzyme activity. K_i is a dissociation constant of an enzyme-inhibitor complex. K_i may be calculated from IC_{50} according to the following equation: $K_i = IC_{50}/(1+S/Km)$.[1] You are correct that K_i is the proper term for expressing activity of a reversible inhibitor. K_i represents a correction of IC_{50} for assay conditions (e.g., substrate concentration). So comparisons among data not collected under exact experimental conditions (ideally in the same assay) are best made using K_i values.

You also state that enzyme inhibition for an irreversible inhibitor should be expressed as EC_{50}. We disagree with this statement. EC_{50} is a term used for agonist effects and is defined as ". . . concentration of drug that produces 50 percent of maximal effect."[2] Inhibitory activity is expressed as IC_{50}. Ulus et al. (1999) expressed MAO-A and MAO-B inhibition for irreversible inhibitors as EC_{50}s, but the reader does not know how the authors calculated EC_{50} from the data given. The legend to Table 2 stated that "the concentration producing 50% inhibition (IC_{50}) was calculated graphically from semilog plots (the concentration-inhibition curve) of inhibitor concentration against percent inhibition." However, the data, as noted, were expressed as EC_{50}s. Perhaps the authors are using EC_{50} and IC_{50} synonymously.

Also, it is not incorrect to express activity of an irreversible inhibitor as K_is. As discussed in scientific literature, in calculating a K_i for an irreversible inhibitor, care must be taken to collect data during the linear portion of the semilog plot of percentage inhibition vs. inhibitor concentration curve.[3] The linear portion of the curve represents formation of the enzyme-inhibitor complex, a reversible phase. Dostert et al. (1989)[4] used K_i values to compare deprenyl's (an irreversible inhibitor) K_i values for MAO-A and MAO-B inhibition with those of reversible MAOIs. According to Dostert et al. (1989), "[a]lthough deprenyl is an irreversible mechanism-based MAOI, its K_i values toward MAO-A and MAO-B can be obtained during the formation of the initial enzyme-inhibition complex and compared with those of reversible MAOIs."

You commented that phentermine's MAOI activity was compared to that of other MAOIs, even though FDA's letter indicated that ". . . a direct comparison was not possible." These

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[1] Chen Y-C, Prusoff WH, *Biochem Pharmacology* 22:3099-3108, 1973.

[2] Katzung BG (ed), *Basic and Clinical Pharmacology* 6th Edition., Appleton & Lange, Norwalk, Connecticut, 1995, pg.11.

[3] Fowler CJ et al., *Biochem Pharmacology* 31(22):3555-3561, 1982.

[4] Dostert et al. , *Med Res Rev* 9(1):45-89, 1989.

comparisons were made with the warning that inhibitory activity was not expressed using the same terms and was not expressed by ignoring the differences in K_i and EC_{50} calculations.

3. You state: "The fact that phentermine is weak at inhibiting MAO is irrelevant. The fact that it can inhibit the enzyme should be enough of a concern. FDA does not distinguish between weak and strong inhibitors in their approval of Patient Package Inserts or any other literature."

From a regulatory perspective, the fact that phentermine may be a *weak* inhibitor of MAO is not irrelevant, but, it is insufficient to simply demonstrate *weak* inhibition of MAO in an in vitro or ex vivo assay. The relevant portion of 21 CFR part 201.57 (content and format of labeling for human prescription drugs) states that the Clinical Pharmacology section should include:

> *a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. (21 CFR 201.57 (b)(1))*

4. FDA's letter denying the citizen petition also cites a letter to *Synapse* from Dr. Richard Rothman. This letter was retracted by Dr. Rothman in a letter to the editor of *Synapse* and was included in the original citizen petition.

We acknowledge that Dr. Rothman's letter was included in the original citizen petition and that Dr. Rothman made a retraction. However, it is important to note that in his letter to the editor (*Synapse* Vol. 33:81, 1999), Dr. Rothman retracted only one statement in his critical appraisal of the phentermine article by Ulus et al. (*Synapse* Vol. 32:141-145, 1999). Dr. Rothman did not retract any of his scientific discussion regarding the issue of phentermine as an MAOI.

5. You assert: "Maximum phentermine levels are reached from two to three hours following oral administration. They then drop off. The Douglas paper that is referred to by Rothman does not indicate the timing of dosing in relation to blood sampling. If the drug levels were administered the day before the sampling, then one would expect low levels."

According to the published article by Douglas et al. (1983),[5] phentermine (phentermine resin, Duromine) was administered at doses of 15 to 60 mg (mean daily dose = 36 mg) for up to 20 weeks. Blood samples were collected "on the 6th and 8th week and on the 16th and 18th week . . . for plasma phentermine concentrations." In other published studies conducted using doses within the range used in Douglas et al. (1983), T_{max} estimates were reported as follows:

- 8 hours (range: 4 to 24 hours; in the case of T_{max} = 24 hours, initial peaks were

[5] Douglas et al., *Int J Obesity* 7:591-595, 1983.

observed at 4 hours and 8 to 12 hours in each of two subjects)[6]

- 11.5 hours (range: 0 to 20 hours, following multiple dosing)[7]
- ≈10 hours[8]
- ≈9 hours[9]
- ≈6 hours (last time point sampled)[10]

Although you are correct that Douglas et al. (1983) did not state the exact time of blood sampling in relation to drug administration, a number of published articles report T_{max} values greater than the 1 to 3 hours postdosing indicated by your clients. Two such studies reported peak levels at ≈24 hours following dosing. The most probable explanation for the discrepancy in the T_{max} estimates is that Douglas et al. (1983) used a phentermine resinate formulation designed to prolong exposure (compared with the hydrochloride form). The T_{max} estimates for the other published studies were also for phentermine resin. Morselli et al. (1978) was the only published study reviewed that reported an apparent T-1/2 for phentermine. Morselli et al. (1978) reported a T-1/2 of 24.6 +- 3.7 hours for phentermine resin. FDA used the data provided by Groenewoud et al. (1993) to calculate a T-1/2 estimate that was approximately 24 hours. Also, plasma data reported by Dadgar et al. (1985) indicated that plasma levels of phentermine 24 hours after a single oral dose of phentermine resin were 30 to 100 percent of the C_{max} (i.e., in 2 cases, the 24-hour value was the C_{max}).

The data from these published studies would suggest that the plasma levels reported by Douglas et al. (1983) may be within 50 to 100 percent of C_{max}, depending upon when the blood samples were collected in relation to dosing and may not, therefore, represent too low an estimate. Even multiplying the mean plasma level for phentermine reported by Douglas et al. (1983) by a factor of 2 or 3 would not substantially change Dr. Rothman's interpretation of the clinical significance of phentermine's in vitro effect on MAO-A.

6. You state that not all clinically useful MAOIs decrease 5-hydroxyindolacetic acid (5HIAA) to the extent that the irreversible MAOIs do. You further state that moclobemide has been reported to produce only a slight decrease (Holford et al.) and this marker may not be that useful when investigating humans (Koulu et al., 1989; Berlin et al., 1990).

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[6] Dadgar D et al., *J Chromatog* 337:136-141, 1985; Ionamin.

[7] Groenewoud G. et al., *Int J Clin Pharm, Therapy, Toxicol* 31(8):368-372, 1993; phentermine resin, Duromine.

[8] Hinsvark ON et al., *J Pharmacokinet Biopharmaceut* 1(4):319-328, 1973; Ionamin.

[9] Morselli PL et al., *Central Mechanism of Anorectic Drugs*. In S. Garattini & R. Samanin (eds), Raven Press, NY, 1978, pp 241-265.

[10] Saletu B, Grunberger J, *J Pharmakpsychiat* 12:45-58, 1979; phentermine resin, Mirapront.

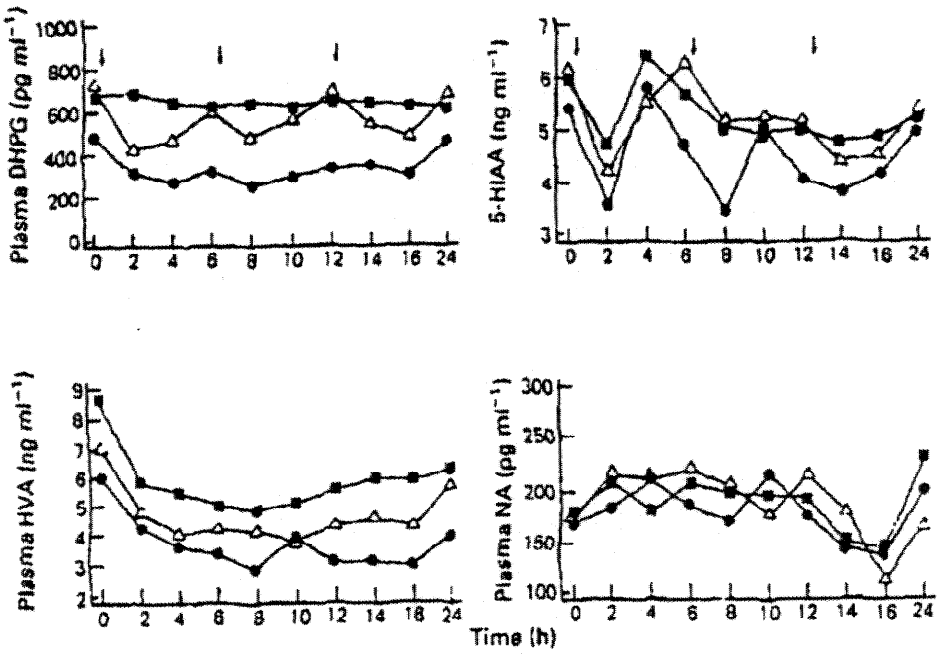

Figure 1 Mean plasma DHPG, HVA, 5-HIAA and noradrenaline concentrations on day 8 after administration of moclobemide (450 mg day^{-1}, •), toloxatone (1000 mg day^{-1}, △) and placebo (■) for 1 week. (Arrows indicate drug intake. S.e. means have been omitted for clarity.)

The published study (Berlin et al., 1990) noted that " . . . the effect of moclobemide on the deamination of 5-hydroxytryptamine (5HT) is known to be moderate . . . probably because the affinity of the drug to the binding sites of the MAO is less than that of serotonin."

Koulu et al. (1989) measured urinary excretion of 5HIAA (in addition to other parameters) in 8 healthy male volunteers following single oral doses of moclobemide (100, 200, and 300 mg). Moclobemide did not significantly affect urinary 5HIAA. Maximum inhibition was 23 percent at the 0 to 3 hours collection period.

Therefore, two of the three published articles you cite demonstrated decreases in 5HIAA with moclobemide. In the study (Koulu et al.) in which a significant decrease in 5HIAA was not reported, urinary, not plasma, 5HIAA was measured.

Other published studies, however, question the usefulness of peripheral 5HIAA as an indicator of in vivo MAOI. For example, Dingemanse et al. (*Clin Neuropharmacol* 19(5):399-414, 1996) measured changes in a number of parameters, including plasma levels of 5HIAA, in healthy volunteers following treatment with moclobemide (200 mg b.i.d.) for 16 days. Dangemanse et al. (1996) reported that moclobemide caused . . . a moderate reduction in DOPAC and 5HIAA plasma concentrations, corroborating the results from previous studies . . ."; however, the effect on 5HIAA did not appear to be statistically significant. Markianos et al. (*Psychiatry Res* 52(3):259-264, 1994) reported no significant change in plasma 5HIAA following administration

of moclobemide (mean final dose: 8.9 mg/kg/day). Another published article (Celada et al., *J Neural Transm* 32:149 – 154 (Suppl), 1990) reported that phenelzine (45 mg/day for 6 weeks) increased plasma 5HT (270% above basal levels) and decreased plasma 5HIAA (22%). The latter effect was not statistically significant.

These studies are certainly not the only ones assessing the effects of various compounds on 5HIAA. However, they do illustrate that plasma 5HIAA may be significantly affected by reversible MAOIs, and that it may not be the most sensitive indicator of in vivo MAOI activity.

III. Labeling of Phentermine

Your position is that current labeling for phentermine is not adequate to ensure the safety of phentermine, and you request that the current language of the labeling and patient insert be changed to read as follows:

> Phentermine is capable of inhibiting monoamine oxidase (MAO) and therefore should not be used concurrently with sympathomimetic amines or selective serotonin reuptake inhibitors (SSRI).

The current approved labeling for phentermine (ADIPEX-P capsules and tablets, Ionamin capsules) states (in the WARNINGS section) that:

> The safety and efficacy of combination therapy with phentermine and any other drug products for weight loss, including selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, fluvoxamine, paroxetine), have not been established. Therefore, co-administration of these drug products for weight loss is not recommended.

Further, the labeling states:

> Primary Pulmonary Hypertension (PPH) . . . has been reported to occur in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine . . .

> Valvular Heart Disease: Serious regurgitant cardiac valvular disease . . . has been reported in otherwise health [sic] persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss . . .

relevant information and views in the [illegible]

In addition, phentermine is contraindicated for use "During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result)."

Consequently, we conclude that the current labeling addresses the concurrent use of phentermine with MAOIs, SSRIs, and sympathomimetic amines and warns against their combined use sufficiently for safe prescribing and therapeutic use.

IV. Conclusion

After a review of the information provided in your reconsideration request, we conclude that the relevant information and views in the administrative record were adequately considered in denying your clients' citizen petition. We also conclude that the data submitted in support of your clients' original petition and reconsideration request were not sufficiently persuasive to cause us to rescind the Agency's decision or to require modification of the language of the labeling and patient insert.

The decision to deny the citizen petition is upheld. If your clients intend to pursue a change in the labeling to reflect the MAOI activity of phentermine, we recommend that they conduct studies to document changes in peripheral indices considered to reflect in vivo MAOI activity following oral administration of phentermine at clinically relevant doses. Your clients should justify their selection of parameters and should not rely on any one parameter. Many studies have been published that discuss the relative value of various parameters.

Sincerely yours,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs