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Food and Drug Administration  
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1600 20th Street, N.W.  
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Re: Docket No. 98P-0561/CP1

Dear Dr. Wolfe, Dr. Sasich, and Dr. Barbehenn:

This responds to your citizen petition submitted July 14, 1998 (Petition), requesting that the Food and Drug Administration (FDA) change the labeling and other sources of information about the drug Viagra (sildenafil citrate) to add information about certain safety concerns. You also maintain that doctors and patients should be informed about the numerous drugs that can cause impotence or other forms of sexual dysfunction to decrease the likelihood that Viagra is used as a treatment for drug-induced sexual dysfunction. FDA is also responding to your letter dated August 20, 1998 ("Letter"), requesting additional labeling changes and calling for a meeting of FDA's Cardiovascular and Renal Drugs Advisory Committee to discuss Viagra.

Subsequent to your submission of this petition, Pfizer, Inc. (Pfizer), the manufacturer of Viagra, significantly revised the product's package insert. Pfizer has added a WARNINGS section that addresses several matters, including the potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Pfizer has also revised the CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS sections of the Viagra package insert. To the extent that these changes effectively provide what you have requested, FDA grants your petition in part. Regarding other matters, the Agency believes that there is insufficient evidence of safety concerns to warrant the labeling changes you requested, particularly your request that Viagra be contraindicated for use in patients with certain specified conditions. Therefore, FDA denies your petition in part. FDA denies your request that the Agency call a special advisory committee meeting to address concerns that you and the joint task force of the American College of Cardiology (ACC) and the American Heart Association (AHA) have raised about Viagra.

#### I. EXCLUSION OF PERSONS FROM CLINICAL TRIALS ON VIAGRA

You ask that Viagra be contraindicated in people with the diseases or conditions that served as a basis for exclusion during the clinical trials. You note that men with certain medical conditions were excluded from participating in the clinical trials of Viagra (Petition at 1-2). Included among these were men with the following conditions: (1) blood pressure of less than

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90/50 or more than 170/100; (2) active peptic ulcer disease or bleeding disorder; (3) any clinically significant baseline laboratory abnormality, need for anticoagulants, androgens, or trazodone (an antidepressant); (4) need for aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) and a history of peptic ulcer disease; (5) history of retinitis pigmentosa; (6) uncontrolled diabetes or diabetic retinopathy; (7) stroke or myocardial infarction within 6 months, cardiac failure, unstable angina, or ECG ischemia; and (8) life-threatening arrhythmia within 6 months.

You note that there is no exclusion in the labeling for Viagra for any of these conditions. You contend that if the clinical trial exclusions were applied to those currently using the drug, the dangers associated with use of the drug would be reduced (Petition at 2).

FDA does not agree that the labeling for Viagra should be revised to contraindicate the use of Viagra in men with conditions that would have prevented their participation in the Viagra clinical studies. The purpose of clinical trials is to obtain clear, unconfounded information on whether a drug is safe and effective in treating a particular disease or condition. For this reason, as well as to provide important protections for research subjects, clinical trials are conducted under very precise and controlled conditions. Not all of these conditions are necessarily applicable to the administration of an approved drug product in general medical use. Physicians have access to the safety and effectiveness information in a drug's package insert and other approved labeling. Because different scientific, medical, and ethical issues are implicated in clinical trials and the practice of medicine, it often is not necessary or even appropriate that the approved product labeling for a drug contraindicate its use in all patients excluded from clinical trials of the drug. However, it is generally important to indicate high risk patient populations in which there are few data from controlled trials.

For each of the conditions that you list, either the current package insert for Viagra provides sufficient safety information or there are other reasons why it is not necessary that use of the drug be specifically contraindicated in patients with such conditions. These reasons are discussed below.

**A. Blood Pressure <90/50 or >170/100; Clinically Significant Baseline Laboratory Abnormality; Uncontrolled Diabetes; Stroke or Myocardial Infarction Within 6 Months; Cardiac Failure; Unstable Angina; ECG Ischemia; Life-Threatening Arrhythmia Within 6 Months**

Pfizer has added a WARNINGS section to the Viagra package insert that addresses most of the above-listed conditions. The WARNINGS section states, in part, that there is no controlled

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clinical data on the safety or efficacy of Viagra in the following groups, and if the drug is prescribed for such patients it should be done with caution:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months
- Patients with resting hypotension (BP < 90/50) or hypertension (BP > 170/110)
- Patients with cardiac failure or coronary artery disease causing unstable angina
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases)

Each of these conditions involves unstable or high-risk, medically ill patients who are inappropriate candidates for participation in most clinical trials. The standard of clinical care for such patients is rigorously conservative. For example, elective surgery is generally postponed when these conditions are present. In addition, most physicians would postpone any treatment of erectile dysfunction — or, for that matter, any elective treatment — until such conditions or others, such as uncontrolled diabetes mellitus, had improved or stabilized. Given this, FDA believes that the added warning adequately reminds physicians of potential concerns associated with administering Viagra to such patients.

Moreover, Pfizer has added the following statements to the WARNINGS section regarding the use of Viagra in patients with preexisting cardiovascular disease:

There is potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg, see **CLINICAL PHARMACOLOGY: Pharmacodynamics**). While this normally would be expected to be of little consequence in most patients, prior to prescribing VIAGRA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

In addition, Pfizer has added the following to the PRECAUTIONS section, Information for Patients subsection:

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who

experience symptoms (e.g., angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.

**B. Active Peptic Ulceration; Bleeding Disorder**

In the PRECAUTIONS section of the Viagra package insert, the subsection titled "General" states that "[t]he safety of VIAGRA is unknown in patients with bleeding disorders and patients with active peptic ulceration." FDA believes that this statement provides sufficient notice that the physician should take these conditions into consideration when deciding whether to prescribe Viagra.

**C. Need for Anticoagulants**

The need for anticoagulation was not an exclusion criterion in all efficacy studies on Viagra. In addition, Viagra's sponsor performed a pharmacokinetic study involving Viagra and warfarin that revealed no significant interaction. The Viagra package insert (PRECAUTIONS section, Drug Interactions subsection) states, "No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9." Similarly, two interaction studies involving Viagra and aspirin revealed no clinically significant interaction. The same subsection of the package insert states, "VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg)." Therefore, FDA believes that the package insert adequately addresses this concern.

**D. Need for Androgens**

The PRECAUTIONS section, General subsection, states that "[t]he evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment." It is a reasonable medical practice to assess a patient for hypogonadism in an evaluation of erectile dysfunction and to begin treatment with androgen if hypogonadism is observed. This practice generally was followed in the clinical trials for Viagra. Patients for whom androgen therapy was not successful were then candidates for other treatments. Because this is a matter of clinical practice rather than a safety issue, it does not warrant revision of the Viagra package insert at this time.

**E. Need for Trazodone**

The package insert (CLINICAL PHARMACOLOGY section, Clinical Studies subsection) describes the efficacy of Viagra in patients with depression and those on antidepressants. Trazodone has been reported to cause spontaneous penile erection (and, rarely, priapism).

Therefore, it should be excluded from use in clinical trials of erectogenic agents because it is a potential confounder of results. However, this does not preclude its use in a clinical setting. It should be noted that physicians have issued millions of Viagra prescriptions (7.5 million in 1998) and there have been no reported adverse events related to trazodone-Viagra interaction. Therefore, FDA does not believe that adding a warning about the use of trazodone to the package insert is warranted.

**F. Need for Aspirin or NSAIDs and a History of Peptic Ulcer Disease**

The clinical trials on Viagra did exclude patients with both a history of peptic ulcer disease *and* a need for aspirin or NSAIDs. Such patients are at clear risk for bleeding ulcers due to the effects of aspirin and NSAIDs as well as their prior history. However, patients with *either* a history of peptic ulcer disease *or* a need for aspirin or NSAIDs were included in the clinical trials. In addition, as stated in the product labeling, "Viagra has no effect on bleeding time when taken alone or with aspirin." Therefore, FDA does not believe that the added theoretical risk of Viagra to a patient with a history of peptic ulcer disease who is taking aspirin or NSAIDs warrants revision of the package insert.

**G. Retinitis Pigmentosa**

Pfizer has revised the WARNINGS section of the package insert to state that there is no controlled clinical data on the safety or efficacy of Viagra on patients with retinitis pigmentosa and that if the drug is prescribed it should be done with caution. A similar statement previously appeared in the PRECAUTIONS section. The Agency believes that this adequately warns physicians about administering Viagra to such patients.

**H. Diabetic Retinopathy**

Viagra was studied in patients with diabetic retinopathy and there were no significant differences reported between these patients and those who did not have this disease. Therefore, no reference to diabetic retinopathy in the package insert is warranted at this time.

**II. SIGNIFICANT LOWERING OF BLOOD PRESSURE**

You state that, in laboratory studies involving animals, sildenafil lowered the blood pressure of 40 percent of the animals and increased the heart rate of 18 percent of them. You note that men with blood pressure of less than 90/50 were excluded from some of the Viagra clinical studies, and you contend that administering Viagra to men with this condition might cause serious problems. In addition, you cite a study in which Viagra produced a significant further lowering of blood pressure in patients already stabilized on amlodipine, a calcium channel blocking drug used to treat hypertension. Finally, you comment that Viagra's effect on blood

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pressure has been identified as a major safety concern and that men who are taking nitrates to control angina should not take sildenafil because the nitrates also affect blood pressure (Petition at 2-3).

As noted above, the WARNINGS section added to the Viagra package insert includes a statement that there is no controlled clinical data on the safety and efficacy of the drug in patients with blood pressure of less than 90/50, and it also warns physicians to consider whether patients with underlying cardiovascular disease could be affected by the vasodilatory effects of Viagra.

Paragraph 2 of the CLINICAL PHARMACOLOGY section, Pharmacodynamics subsection, now begins with the heading "Effects of VIAGRA on Blood Pressure" and reads as follows:

Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease of 8.4/5.5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg of VIAGRA, therefore the effects are not related to dose or plasma levels. Larger effects were recorded among patients receiving concomitant nitrates (see CONTRAINDICATIONS).

Paragraph 3 of the Pharmacodynamics subsection now begins with the heading "Effects of VIAGRA on Cardiac Parameters" and reads as follows:

Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

Studies have produced relevant data on the effects of VIAGRA on cardiac output. In one small, open-label, uncontrolled, pilot study, eight patients with stable ischemic heart disease underwent Swan-Ganz catheterization. A total dose of 40 mg sildenafil was administered by four intravenous infusions.

The results from this pilot study are shown in Table 1; the mean resting systolic and diastolic blood pressures decreased by 7% and 10% compared to baseline in these patients. Mean resting values for right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure and cardiac output decreased by 28%, 28%, 20% and 7%, respectively. Even though this total dosage produced plasma sildenafil concentrations which were approximately 2 to 5 times higher

than the mean maximum plasma concentrations following a single dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

Finally, additional wording (see italics) was added to the last paragraph of the CLINICAL PHARMACOLOGY section, Clinical Studies subsection, as follows: "Analysis of the safety database showed no apparent difference in the side effect profile in patients taking VIAGRA with and without antihypertensive medication. *This analysis was performed retrospectively, and was not powered to detect any pre-specified difference in adverse reactions.*"

Because of these statements in the CLINICAL PHARMACOLOGY and WARNINGS sections of the Viagra package insert, FDA does not believe that it is necessary that the drug be specifically contraindicated in patients with blood pressure of less than 90/50.

Pfizer has added to and revised the package insert statements about effects on blood pressure observed during the use of Viagra with amlodipine. In the PRECAUTIONS section, Drug Interaction subsection, the insert now states: "When VIAGRA 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic." The following paragraph was added to the PRECAUTIONS section, General subsection: "Patients on multiple antihypertensive medications were included in the pivotal clinical trials for VIAGRA. In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and VIAGRA, 100 mg, were orally administered concomitantly to hypertensive patients, mean additional blood pressure reductions of 8 mmHg systolic and 7 mmHg diastolic were noted (see Drug Interactions). Controlled studies of drug interaction between VIAGRA and other antihypertensive medications have not been performed." The Agency concludes that these labeling statements provide sufficient protection for amlodipine patients for whom a physician is considering prescribing Viagra.

With respect to your concern about administering Viagra to patients taking nitrates to control angina, the original approved package insert stated the following in the CONTRAINDICATIONS section: "Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are concurrently using organic nitrates in any form is therefore contraindicated." Pfizer has further enhanced this statement contraindicating Viagra in patients taking nitrates, as follows:

Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using

organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL) (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism). In the following patients: age > 65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatine clearance < 30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.

FDA believes that these CONTRAINDICATIONS statements adequately advise against the use of Viagra in patients taking nitrates to control chest pain.

### III. EFFECTS ON VISION

You note that the package insert for Viagra states that adverse effects involving abnormal vision (such as a color tinge, increased sensitivity to light, or blurred vision) appeared in some studies of the drug. Although you point out that the most serious and common vision abnormalities occurred at doses greater than the recommended maximum dose (100 mg/day), you add that taking more than one dose per day was the most common protocol violation. You state that there are "unregulated patient information leaflets currently being dispensed with Viagra" instructing patients to "Take only as directed, usually once daily as needed." You contend that if this leaflet accompanies a prescription for the 100 mg dosage form of Viagra, the directions for patients inadequately warn against taking more than 100 mg of the drug each day (Petition at 3-4).

FDA believes that the Viagra package insert adequately discusses the findings of vision abnormalities and describes the dose relationship associated with these effects. The CLINICAL PHARMACOLOGY section, Pharmacodynamics subsection, now states as follows under "Effects of VIAGRA on Vision":

At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This

finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, electroretinograms, intraocular pressure, or pupillometry.

The ADVERSE REACTIONS section, Pre-Marketing Experience subsection, notes the following: "In fixed dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently." In the Post-Marketing Experience subsection, Pfizer has added the following: "Ocular: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema."

The DOSAGE AND ADMINISTRATION section states that the "maximum recommended dosing frequency is once per day." If you believe that unapproved labeling is being distributed with Viagra that characterizes the recommended dosage as "usually once daily," we request that you submit such labeling to the Center for Drug Evaluation and Research's Division of Drug Marketing, Advertising, and Communications for review and evaluation.

#### **IV. DRUGS THAT CAN CAUSE SEXUAL DYSFUNCTION**

You question whether patients would choose to take sildenafil to treat the sexually-related adverse effects (e.g., loss of desire, inability to maintain an erection, and other forms of sexual dysfunction) of another drug if they were fully aware of the problem, especially if there were an alternative drug (or a lower dose of the same drug) that did not cause sexual dysfunction. You contend that of 69 adverse reaction reports involving patients taking one or more drugs in addition to Viagra and fully listing such drugs, about 46 percent include one or more drugs known to cause sexual dysfunction. You also claim that in 36 percent of the 75 reports involving patients taking one or more drugs in addition to Viagra, at least one of these drugs was for treating cardiovascular diseases, some of which are themselves associated with increased sexual dysfunction. You argue that to worsen preexisting sexual dysfunction and treat it with Viagra rather than to try to lower the dose of the offending medication or to substitute another drug less likely to cause such dysfunction "seems to be an unwise medical decision, if indeed it is being made with full knowledge" (Petition at 4-5).

FDA agrees with your view that where a patient's drug therapy is a likely cause of sexual dysfunction, physicians should consider reduced dosage or a change of therapy before prescribing Viagra to treat the sexual dysfunction. It is not clear, however, how often erectile dysfunction is caused by the drugs listed, even if a drug is associated with sexual dysfunction on some occasions. Moreover, in many cases, removing a potentially responsible medication

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will not be feasible or desirable. Elimination of beta-blockers, diuretics, calcium channel blockers, spironolactone, amiodarone, digoxin, or antidepressants, for example, may not be in patients' interest.

As noted above, the first statement in the PRECAUTIONS section, General subsection, cautions that any evaluation of erectile dysfunction should include a complete medical assessment to determine potential underlying causes and to identify appropriate treatment. FDA also notes that the package insert (CLINICAL PHARMACOLOGY section, Clinical Studies subsection) addresses the efficacy and safety of Viagra in treating men taking other medications, including types of drugs known to produce side effects involving sexual dysfunction, such as antidepressants/antipsychotics and antihypertensives/diuretics. In short, the Agency believes that this issue is a matter of clinical practice that should be determined by individual physicians.

**V. LABELING CHANGES RECOMMENDED IN YOUR AUGUST 20, 1998, LETTER**

**A. Pregnancy Warnings**

You maintain that because Viagra is already being used off-label by women of childbearing potential and because experiments in women are about to begin, the label must include accurate information about pregnancy risks. You contend that the current label falsely states that sildenafil belongs in Pregnancy Category B. You believe that the drug belongs in Category C because there are rabbit and rat studies that have shown an adverse effect on fetuses but there are no adequate studies in humans (Letter at 3-4).

FDA believes that pregnancy category B is appropriate for Viagra because there is no evidence of selective animal reproduction toxicity. FDA evaluated the rabbit and rat studies in accordance with 21 CFR 201.57(f)(6)(i)(b), which states that a drug should be placed in Pregnancy Category B if animal reproduction studies have failed to demonstrate a risk to the fetus and there are not adequate and well-controlled studies in pregnant women.

In the rat and rabbit embryo fetal development studies performed at oral doses of up to 200 mg/kg, sildenafil showed no teratologic effects at approximately 27 and 48 times, respectively, the oral clinical dose of 100 mg per day on the basis of mg/M<sup>2</sup> body surface area, assuming a 70 kg man. Concerning the rat pre- and postnatal development study performed at up to 60 mg/kg, FDA regards the findings of dilated ureters and hydroureters in the first generation, as well as of distended bladder in the second generation, as spontaneously appearing minor abnormalities. Only at the maternal dosage of 60 mg/kg was there observed a slight decrease in live birth rate and an increase in incidence of dilated ureters in the nonviable pups. Furthermore, in the treated first generation pups that died during lactation or were sacrificed at

weaning, there was no excess incidence of ureteral or renal pelvic dilatation even at the high dose of 60 mg/kg. This maternal dose of 60 mg/kg represents approximately 40 times the total unbound drug and metabolite  $AUC_{1-24hr}$  0.105 ug.hr/ml of a 70 kg man treated with the maximum recommended daily dose of 100 mg sildenafil. FDA concludes that the rat multiple of the proposed maximum recommended human dose projects adequate safety for humans. Therefore, the Agency sees no need to revise the package insert statements placing Viagra in Pregnancy Category B.

## **B. Genotoxicity**

You contend that a warning about genotoxicity should be added. You state that the first definitive assay with human lymphocytes produced statistically significant increases in the number of cells with multiple chromosomal aberrations and that a repeat study was negative. Your position is that the overall results are equivocal rather than negative as stated by Pfizer (Letter at 5).

FDA evaluated four genotoxicity studies with sildenafil and concludes that the drug showed no genotoxic potential. The results of the in vitro assay for the detection of chromosomal aberrations in human lymphocytes showed that after 3 hours of exposure to sildenafil at the three concentrations tested with exogenous metabolic activation, there was an increase in the number of cells with chromosomal aberrations (chromatid breaks) when compared to the solvent control. However, this difference was judged not meaningful because the increase in the chromatid breaks was not dose-related and there were only a small number of chromosome breaks that appeared at the two highest concentrations of the drug tested. The incidence of 2 to 2.5 percent aberrant cells in drug treated groups was at or just slightly above the upper limit percentage range of abnormal cells for the historical controls (i.e., 2 percent). Furthermore, these findings were not reproducible in the repeat assay.

From the data reviewed, FDA concludes that there was a very weak aberrational response ( $p < 0.05$ ) compared to solvent control in only one of the two assays and at the low concentration. The slight increase in chromosome aberrations did not fulfill one of the criteria for a positive response in that the findings were not reproducible. Because the criteria for a positive finding were not met, the assay was considered negative for sildenafil in agreement with the conclusion of the drug sponsor.

In addition, there was no statistically significant increase in cells with chromosomal aberrations when sildenafil without metabolic activation was added for the final 24 hours of incubation. Moreover, in vivo genotoxicity and carcinogenicity tests in two animal species with sildenafil were negative. For these reasons, the Agency sees no need to add a warning about genotoxicity.

**C. Priapism**

You note that the Viagra package insert states that no cases of priapism were reported, but you point out that, as of June 30, 1998, there had been at least six adverse event reports involving priapism. You request that these be listed as adverse events on the package insert (Letter at 5).

Pfizer has added a statement in the WARNINGS section of the package insert about the risk of priapism. The statement reads as follows:

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

In addition, a statement has been added to the PRECAUTIONS section, Information for Patients subsection, instructing physicians to warn patients about the dangers of prolonged erections and priapism. Finally, as you requested, the ADVERSE EVENTS section has been revised to include prolonged erection and priapism among the events observed in the postmarketing experience.

**D. Periarthritis**

You state that there is no information in the Viagra package insert that addresses the findings of periarthritis that occurred in rats and dogs (Letter at 5).

Your definition of periarthritis as "severe inflammation of blood vessels" is incorrect because not all periarthritis is severe. All drugs are potentially toxic and the safety margin is the difference between the therapeutic dose and the toxic dose. The dose at which arteritis was found in dogs was 48 times the human exposure, and the no-observable-effect level (NOAEL) dose of 10 mg/kg was 8 times the human exposure. This provided the basis for determining that sildenafil is safe at the recommended doses. Also, your statement that periarthritis occurred in both rats and dogs requires clarification. In rats, a mesenteric arteritis was found in 2 of 10 mid-dose (45 mg/kg/day) males and in 1 of 10 high-dose (200 mg/kg/day) males after 1 month of treatment, but these findings were not reproduced in studies that used higher doses or that were of much longer duration.

You also claim that most toxicological findings in FDA's pharmacology review lacked complete descriptions, thereby making analysis difficult (Letter at 5). You maintain that a fuller description of the toxicity studies appears justified because the findings on arteritis

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occurred in two species and are serious (Letter at 6). You add that if the findings are of sufficient extent and severity, a section in the package insert on animal toxicity may need to be added.

Most toxicological findings did not lack complete descriptions. A substantial effort was made to document and summarize the toxicology study findings with text, detailed tables, and figures. Regarding the specific studies you cite, the pharmacology review provided a complete description of the periarteritis observed in the 1-year dog study. The review noted that in males, the periarteritis involved the heart and other organs (they were not listed due to the length of the list). The affected tissues in males were the heart (right coronary groove and right atrium), thyroid, esophagus, thymus, stomach, and epididymides. As for the 6-month dog toxicity study, a disseminating necrotizing panarteritis (involving multiple tissues) was seen in only 1 of 4 high-dose males and in none of the females. Organs affected in the single male were the thymus, mediastinal lymph node, esophagus, thyroid, epididymides, spinal cord meninges, and eyes (optic nerve meninges). Complete unilateral testicular infarction, possibly the most serious finding, may have been a consequence of the arterial pathology. However, these effects occurred only after high exposure and did not occur in any of the other animals in the other dose groups. Consequently, they were not considered to be relevant to humans receiving sildenafil at therapeutic doses.

Regarding the 1-month oral rat toxicity study, the sponsor described the findings of mesenteric arteritis as follows:

Arteritis, characterized by variable degree of medial necrosis and perivascular infiltration of mixed inflammatory cells, was observed in the medium-sized renal and mesenteric arteries, the latter being observed in the sections of mesenteric lymph nodes. The lesion was diagnosed in the kidney of one animal of each male group, including control, and in the mesenteric arteries of 2 animals of the mid-dose male group and one animal of the high-dose male group.

Because a consistent pattern of arteritis was not observed in the rat study, FDA's pharmacology review did not address the relationship between the mesenteric arteritis found in the rat study and the arteritis found in many of the dog studies. As for why FDA's review provided no information on whether the findings from the 1-month intravenous rat toxicity study might be related to the findings from other studies, FDA concluded that this was not necessary because no clear dose effect for myocardial inflammation was apparent from the results of the rat study. The Agency concluded that the relationship of these findings to the arteritis observed in either the dog or rat studies was not evident, and that they were probably unrelated. The 30 percent incidence of myocardial inflammation in the control rats may indicate either an underlying infection or the use of non-sterile techniques for repeated

intravenous injection. This lesion was not found in the 13-day intravenous study in rats or in any of the oral studies in rats or dogs.

FDA agrees that findings of arteritis in any species should be taken seriously. The findings of arteritis in dogs were consistent and reproducible, and were addressed in the Agency's pharmacology review. In rats, however, the findings were restricted to a single one-month study in 2 of 10 mid-dose (45 mg/kg/day) and 1 of 10 high-dose (200 mg/kg/day) male rats. Arteritis was not described in any of the other rat studies that were of shorter or longer duration.

The findings of arteritis in dogs were a clinical concern, but it is not unusual for drugs to have severe toxicities associated with their use when given in very high doses. FDA expended substantial effort in the pharmacology review to determine a safety margin. Regarding arteritis in dogs, FDA determined that a 49-fold multiple of the human exposure at the lowest arteritis-producing dose of 50 mg/kg/day and an 8-fold multiple of the human exposure at the NOAEL was an appropriate safety margin for use in humans. The findings of arteritis in rats were difficult to interpret because of their lack of reproducibility.

In summary, FDA concluded that it was unnecessary to include a section in the Viagra package insert on animal toxicity because of (1) the higher doses and exposures required to produce the effects in animals and (2) the longer continuous duration of use in the animal studies compared to human administration. Unless new clinical or preclinical information on sildenafil-induced arteritis becomes available, the Agency sees no need to revise the labeling.

#### **E. Effects of Phosphodiesterase (PDE) Inhibition on Vision**

You contend that, although the Viagra labeling cautions about the use of the drug in patients with retinitis pigmentosa, it fails to explain that visual problems more severe than just "blue" vision may be possible. Specifically, you contend that Viagra's inhibition of phosphodiesterase (PDE) may result in the production of high levels of cyclic guanosine monophosphate (GMP), which can lead to retinal degeneration (Letter at 6). You are concerned that when Viagra is taken repeatedly, cyclic GMP may rise to toxic levels in some individuals (*id.* at 7). You ask how vision will be monitored in patients using Viagra and whether people with preexisting retinal diseases are at increased risk of further retinal damage.

Pfizer has revised the CLINICAL PHARMACOLOGY section, Pharmacodynamics subsection, to state, in part, that "[a]n evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, electroretinograms, intraocular pressure, or pupillometry." As for the risk of retinal degeneration due to high levels of cyclic GMP, FDA does not believe that there is evidence of such a possibility. The repeated use of Viagra over as much as 1 year in clinical trials did not

demonstrate any serious ophthalmologic adverse events. In addition, despite extensive use of Viagra since its approval, FDA has received few reports of serious ophthalmologic adverse reactions. Consequently, the Agency sees no need at this time to require further labeling changes related to visual problems.

## **VI. REQUEST FOR ADVISORY COMMITTEE MEETING**

You ask that FDA immediately convene a meeting of its Cardiovascular and Renal Drugs Advisory Committee to discuss concerns about Viagra (Letter at 1). You state that this is especially urgent because a joint task force of the American College of Cardiology (ACC) and the American Heart Association (AHA) has issued an interim report expressing concerns about the risks of Viagra for certain categories of patients with cardiovascular disease. These categories are as follows: (1) patients with active coronary ischemia who are not on nitrates; (2) patients with congestive heart failure, borderline low blood pressure, and borderline low volume status; (3) patients on a complicated multidrug, antihypertensive program; and (4) patients on drugs (e.g., erythromycin, cimetidine) or who have conditions (e.g., liver or renal disease) that can prolong the half-life of Viagra (Letter at 1-2). You contend that FDA and its advisory committee should immediately address the implications of the ACC/AHA report, as well as the issues raised in your citizen petition.

FDA believes that the November 1998 labeling revisions adequately address the concerns raised in the ACC/AHA report. As noted above, these changes include the following: new information about the direct effects of Viagra on cardiac function and blood pressure; a new warning about the types of patients on whom no efficacy or safety data is available; new information about the plasma levels of Viagra and their implications for concomitant dosing with nitrates; and a new subsection on adverse reactions in the postmarketing period that includes reports of cardiovascular events. Consequently, FDA believes that the current package insert provides accurate and useful information for the safe and effective use of Viagra.

In addition, FDA's Division of Reproductive and Urologic Drug Products has received assistance from within and outside the Agency to completely address the concerns noted in the ACC/AHA report. This includes consultations with the Agency's Office of Post-Marketing Drug Risk Assessment and the Division of Cardio-Renal Drug Products, as well as consultations with two university-based academic cardiologists acting as Special Government Employees.

For these reasons, FDA does not believe that it is necessary to hold an advisory committee meeting on Viagra at this time. However, should new information emerge on the safety of Viagra that warrants convening the advisory committee, FDA will do so.

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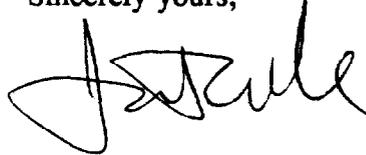
## VII. CONCLUSION

FDA has carefully reviewed the arguments you have raised in support of revising Viagra's package insert. As noted above, Pfizer has made several revisions to the package insert that address some of your concerns. However, to the extent that you request further additions to the CONTRAINDICATIONS section and other modifications to the current labeling, FDA denies your request for the reasons set forth above.

FDA also denies your request that the Agency schedule a meeting of the Cardiovascular and Renal Drugs Advisory Committee to address your concerns and those raised by the ACC/AHA task force. However, the Agency will continue to monitor closely all adverse reaction reports on Viagra and will take appropriate action if warranted by further information.

The Agency also requests that you submit to the Division of Drug Marketing, Advertising, and Communications any unapproved labeling that you believe is being distributed with Viagra that mischaracterizes the recommended dosage stated in the approved package insert.

Sincerely yours,

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

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research