**City and County of San Francisco** **Department of Public Heal**

**Petition to the Food and Drug Administration to change the labeling and take further action to address the association of Viagra (Sildenafil) use and increased STD transmission, including HIV infection.**

July 12, 2004

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

To Whom It May Concern:

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act 21, U.S.C. Section 502(a), and 21 C.F.R. 10.30, to request the Commissioner of the Food and Drugs to change the labeling and other sources of information about Viagra (Sildenafil; Pfizer Inc., New York, NY) to add important information about the drug's association with increased STD transmission, including HIV infection, and to take further steps including patient and physician awareness and education, a change in the drug's marketing, and classification of Viagra as a controlled substance, in order to appropriately address this public health issue.

On March 27, 1998, the Food and Drug Administration approved Viagra, the first oral pill to treat erectile dysfunction. Since this approval, Viagra has become one of the most popular prescription drugs in America, with sales of an estimated $1.7 billion in 2004.[i] Though Viagra is effective at treating erectile dysfunction, new information has arisen regarding an association between Viagra use and sexually transmitted disease (STD) transmission. Numerous studies have been published establishing an association between Viagra use and greater numbers of recent sex partners, higher levels of unprotected anal sex with HIV-positive partners, and higher rates of new STDs, including HIV infection.

In addition, multiple studies have found the use of Viagra outside of medical supervision to be common, with rates as high as 31% among men who have sex with men (MSM).[ii] The President's Council on Bioethics stated in a 2003 report that, "Viagra, a remedy devised for male impotence, is increasingly used by the non-impotent to enhance sexual performance."[iii] This use of Viagra outside of medical supervision and to enhance sexual performance, rather than for the treatment of erectile dysfunction, is referred to as recreational use. Viagra is widely available for sale illegally on the Internet, and use of Viagra in combination with other "club drugs" such as methamphetamines and ecstasy is common. Over time, Pfizer's marketing focus for Viagra has shifted towards healthy, middle-aged men, shifting focus away from its FDA-approved intended use of treating erectile dysfunction. In 2002, the Centers for Disease Control reported an increase in

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STD PREVENTION & CONTROL SECTION 1360 Mission Street, Suite 401 San Francisco, CA 941

several STDs in the United States, including Chlamydia and Syphilis.[iv] From 1999 to 2002, the CDC reported increases in HIV diagnoses in 29 states among MSM.[v] Though Viagra use is most likely not directly responsible for these increases, its association with STD transmission and common recreational use may very well be contributing to the recent resurgence in STD levels, particularly among specific populations. Based upon the association of Viagra use and STD transmission, including HIV infection, as well as the prevalent rates of off-prescription use, substantial action must be taken by the FDA to make Viagra users and physicians aware of this association and to reduce the use of Viagra for unintended purposes.

## A. Statement of Grounds

### Viagra Use and STD Transmission

Numerous researchers, using a variety of patient populations, have established an association between Viagra use and STD transmission, including gonorrhea, syphilis, and HIV infection. While it is unlikely that Viagra directly causes these infections, the increased duration of erection, increased blood flow, and increased mucosal susceptibility may increase the risk of acquiring these infections if having sex with an infected partner. A study exploring the potential role of Viagra in the resurgence of new STD and HIV transmission looked at a population of MSM seeking public STD services in San Francisco, CA. Viagra users were found to have a higher average number of sex partners in the past 2 months compared with non-users (5.4 partners vs. 3.5 partners, $P<0.01$). Among HIV negative men, a greater percentage of Viagra users reported recent unprotected anal sex with a partner of unknown HIV status compared with non-users (30% vs. 15%, $P=0.03$). Using logistic regression, Viagra use was found to be independently associated with an increased number of partners and was also associated with having a new STD diagnosis after controlling for the number of partners.[vi]

Focusing more specifically on HIV transmission, researchers analyzed HIV seroconversions among anonymous male repeat clients at an HIV clinic in San Francisco, CA. HIV incidence was significantly higher among Viagra users compared to non-users (4.4 HIV incidences per 100 person years vs. 1.2 per 100 py, $P<0.001$). In multivariate analysis, Viagra users were more than twice as likely to be diagnosed with HIV than non-users (Odds Ratio 2.5, 95% Confidence Interval 1.5-4.1), with particularly high risk among MSM using both Viagra and amphetamines.[vii]

Numerous studies have found Viagra use to be associated with increased sexual risk behavior. A community based survey study among men who have sex with men in San Francisco found Viagra users to be more than twice as likely to have unprotected anal sex with partners of unknown HIV status than non-users (OR 2.45, 95% CI:1.40-4.32). In multivariate analysis, recent Viagra use was independently associated with having unprotected anal sex with a partner of unknown HIV status.[viii] In a cross-sectional survey looking at gay men in London gyms, HIV-negative men who had taken Viagra in the previous 3 months were significantly more likely to report unprotected anal intercourse

with a partner of unknown HIV status while on Viagra than HIV-negative men who had never used Viagra (8.0% vs. 1.4%, P<0.01).[ix]

In a study looking at drug use and sexual risk behavior among MSM who attend circuit parties, multivariate analysis found Viagra users to be almost four times as likely to have unprotected anal sex with a partner of opposite or unknown HIV status than non-users (OR 3.8, 95% CI 2.0-7.3).[x] A national study looking at substance use and high-risk sexual behavior among MSM using the Internet found Viagra users to be more than three times as likely to have more than 10 sex partners compared with non-users (OR 3.53).[xi] Viagra use in combination with other drug use, particularly methamphetamine, has been found to be associated with a particularly high level of sexual risk behavior. In a cross-sectional sample of MSM in San Francisco, methamphetamine users were twice as likely to have unprotected receptive anal sex compared with non-users (OR 2.03, 95% CI=1.09-3.76), while Viagra users were more than six times as likely to engage in unprotected insertive anal sex than non-users (OR 6.51, 95% CI=2.46-17.24).[xii] These findings establish an association between Viagra use and sexual risk behavior, correlating use of the drug with increased transmission of STDs.

Studies looking at different patient populations have found similar data, validating the association between Viagra use and STD transmission. In Seattle, researchers found MSM Viagra users to be more than four times as likely to have unprotected anal intercourse with a partner of positive or unknown HIV status (OR=4.4, 95% CI:1.7-11.3).[xiii] In Baltimore, a study of MSM at a gay men's clinic found Viagra users to be almost twelve times more likely to engage in high-risk behavior for HIV infection (OR 11.90, P=0.02).[xiv] A published report explored the possibility that Viagra may be contributing to the transmission of HIV among older adults, due to their lack of knowledge about HIV infection or other STDs.[xv] Though further information among more varied patient populations would be beneficial, these similar findings among different patient populations confirm the association of Viagra use and STD transmission.

**Prevalent Recreational Use of Viagra**

The current information about Viagra use and STD transmission becomes even more foreboding given the current data showing prevalent recreational use of Viagra. Numerous studies have shown that Viagra is commonly used outside of physician supervision and for purposes other than its intended use of treating erectile dysfunction. This recreational use becomes even more risky given that it is commonly used with other recreational drugs, such as amphetamines, ecstasy, and gamma-hydroxybutyrate (GHB). As amphetamines and ecstasy can lessen a male's ability to have an erection, Viagra is often taken in combination with these substances in order to allow the user to function sexually. Viagra is also used with these drugs to heighten the sexual experience, enabling the user to have a prolonged erection and multiple partners. This usage is particularly troublesome given the fact that the user is under the influence of these substances, and thus has impaired decision-making capabilities in regards to prevention of STDs. This common recreational use of Viagra, along with the increased STD transmission among

Viagra users, creates a public health problem that requires immediate action by the FDA in order to prevent further increases in STD transmission, including HIV infection.

In a community-based anonymous survey of MSM in San Francisco, 32% had ever used Viagra, with 21% using within the last 6 months. Viagra use was commonly used with other drugs, with 36% of Viagra users combining use with other drugs such as amphetamines (23%), ecstasy (18%), ketamine (11%), and GHB (8%). Of additional concern was Viagra use in combination with amyl-nitrates (11%), a contraindication on Viagra's labeling due to possible severe decreases in blood pressure. The majority of Viagra users did not obtain the drug from a physician (56%); 44% received the drug from a friend, 6% from the Internet, 4% on "the street," and 10% from "other sources."[xvi]

A study looking at men seeking public STD services in San Francisco, CA reported 17% of men using Viagra in the past year. MSM were significantly more likely to use Viagra (31%) than heterosexual men (7%, $P<0.01$). Among the MSM participants, over half of them (56%) had received the Viagra from a friend, rather than from a healthcare provider (42%). Viagra was commonly used with other drugs, such as ecstasy (43%), methamphetamines (28%), and amyl nitrate (15%). Participants mixing Viagra with other drugs were significantly more likely to have received Viagra from a friend (73% vs. 39%, $P<0.01$), and believed that combining Viagra with other drugs enhanced their sexual experience (73% vs. 25%, $P<0.01$).[xvii]

Other studies have found similar levels and patterns of recreational Viagra use. In a cross-sectional survey looking at gay men in London gyms, 15% of participants had ever taken Viagra, 12% had used Viagra more than once, and 9% had used Viagra in combination with other recreational drugs. Among Viagra users, only 17% of users had been prescribed Viagra by a healthcare provider, while 83% had used it outside of medical supervision.[xviii] In a study looking at drug use and sexual risk behavior among MSM who attend circuit parties, 12% of attendees had used Viagra at a circuit party within the past year.[xix]

Viagra use has also been found when focusing specifically on MSM who use methamphetamines. In a cross-sectional study of MSM attending the San Francisco municipal STD clinic, methamphetamine users were more than three times as likely to use Viagra (OR 3.5, 95% CI 2.9-4.4) and reported, on average, having 5 sexual partners during the previous four weeks compared with 2 sexual partners for non-users ($P<0.05$).[xx] Another cross-sectional study of MSM in San Francisco found Viagra use among amphetamine user to be 6%.[xxi] The current body of data regarding recreational Viagra use suggests that off-prescription use is common among numerous groups.

In addition to published data, information from the media and the Internet supports both increased use of Viagra recreationally and association with increased sexual risk behavior. Articles published in the New York Times, the Wall Street Journal, Time Magazine, Newsweek, and many other publications have commented on the common use of Viagra in association with other "club drugs," such as amphetamines and ecstasy. A recent article in the Chicago Tribune wrote of "the new young face of Viagra abuse," as

several physicians chronicled the prevalent use of Viagra among college-aged, heterosexual men that use the drug for sexual enhancement, often in association with other substances.[xxii] In the articles, Viagra users reported getting the drug from friends, sampling, and oftentimes the Internet. Viagra and other ED treatment drugs are readily available on the Internet without a prescription. A recent report estimated that approximately 150 distinct companies, none of whom were the manufacturer, ran between 4,500 and 15,000 websites offering Viagra for sale, with over 1,000 prescriptions sold per day.[xxiii] This gives users another accessible route for acquiring the drug outside of the care of a healthcare provider, increasing the chance for misuse.

The prevalent recreational use of Viagra has been brought to the attention of Pfizer on numerous occasions, though no substantial response has occurred. The FDA's "Intended Use" regulation holds drug manufacturers accountable for use of their product outside of its intended purposes; in this case, for use of Viagra for sexual enhancement rather than for treating erectile dysfunction. 21 C.F.R. § 201.128 states:

> If a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.[xxiv]

At this time, Pfizer has not properly responded in accordance with this regulation, though they have been made aware of the ongoing usage of Viagra for reasons other than its intended use. The FDA must hold Pfizer accountable for the current state of prevalent recreational Viagra use, particularly given the established association between Viagra use and STD transmission.

**B. Action Requested**

The FDA must take immediate steps to target the ongoing public health problem of Viagra use and STD transmission, including HIV infection. The FDA has a responsibility to abate risk-associated abuse, which has been clearly shown in the case of Viagra. The FDA should hold a hearing to discuss the current information regarding the subject, and to develop a plan of action to stem this preventable risk. In addition, though the current data focuses specifically on Viagra, similar action should be taken against Cialis (Tadalafil, ICOS Inc., Bothell, WA) and Levitra (Vardenafil, Glaxosmithkline Inc., Philadelphia), as the associations found with Viagra would likely occur in drugs with identical mechanisms. Specifically, we would like to see the FDA:

**1) Amend the product label of Viagra to state, "The use of VIAGRA increases the risk for new sexually transmitted diseases, including HIV infection."**

Current labeling of Viagra insufficiently addresses the established association between Viagra use and increased STD transmission. Currently, the full prescribing information for Viagra states:

> The use of VIAGRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

Current patient product information for Viagra states:

> Use of this medicine will not prevent the spread of sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV).

This labeling is inadequate given the current level of data on the association between Viagra use and STD transmission. This updated product label makes clear the established association. Given the high level of recreational Viagra use for sexual enhancement rather than for the intended use of erectile dysfunction, it is recommended that the above amended product label be made a black box warning on all product labeling and packaging. In the past, the FDA has added black box warnings to a number of drugs to prevent scientifically unjustified use. The recommended product label would be:

**The use of Viagra increases the risk for new sexually transmitted diseases, including HIV infection.**

The current level of data suggests a prevalence of off-label use, and a black box warning making clear the association between Viagra use and STD transmission is warranted, particularly given the high level of use outside of the care of healthcare providers.

**2) Promote education and awareness among physicians and Viagra users as to the association between Viagra use and STD transmission.**

The current data regarding the prevalent recreational use of Viagra suggests a lack of knowledge among physicians and Viagra users as to the association between use of the drug and STD transmission. Though amendment of the product labeling is fundamental in increasing knowledge of the association, education and awareness towards both physicians and Viagra users is instrumental in targeting this ongoing public health problem. A letter from the Pfizer, in association with the FDA, should be written to physicians detailing the association between Viagra use and STD transmission, including HIV infection. This letter should be similar in nature to the letter written in 1998 by Pfizer updating physicians to the new and expanded safety information regarding Viagra. This letter would be effective in making physicians aware of the current association between Viagra use and STD transmission, including HIV infection.

In addition to physician awareness, Viagra users need to be made directly aware of the current association, particularly given the large percentage of Viagra use occurring outside of the care of healthcare providers. Pfizer needs to create new marketing materials, direct-to-consumer advertising, and educational efforts to address the

recreational use of Viagra in persons at particular risk for STDs, namely men who have sex with men. Effective programs on primary prevention and regular STD check-ups focusing on this at-risk population are urgently needed. Pfizer currently provides Viagra samples in a "six-pack." To promote safer sex, this "six-pack" should contain a "six-pack" of condoms. In addition, prevention and educational programs focusing on the ongoing problem of Viagra use mixed with other drugs such as methamphetamines, nitrates, GHB, and ecstasy are warranted.

**3) Change the marketing strategy of Pfizer Inc. for Viagra to reflect current approved usage of the drug.**

Since its approval in 1998, the marketing of Viagra has gradually shifted towards targeting healthy, middle-aged men. While earlier campaigns used elder spokesmen such as Bob Dole explicitly discussing erectile dysfunction, the approved usage of the drug, current campaigns are increasingly focused on marketing a sexual enhancement image. By sponsoring NASCAR driver Mark Martin and Major League Baseball player Rafael Palmeiro, Viagra's advertisement have shifted away from the intended use of the drug. The FDA's Division of Drug Marketing, Advertising, and Communications must look into Pfizer's current marketing campaign to ensure the company is within regulation for direct-to-consumer advertisements. The amended product label suggested above should be made clear on all advertisements for the drug, in part to reach the established prevalence of recreational Viagra users receiving the drug outside of the care of healthcare providers.

**4) Classify Viagra as a Schedule III Controlled Substance to prevent prevalent recreational use and illegal sales of the drug.**

Current data suggests that Viagra is commonly used recreationally without prescription. In addition, a burgeoning Internet market adds to the accessibility of Viagra for non-prescription users. An effective step to reduce this increased recreational use is to classify Viagra as a Schedule III Controlled substance. The Controlled Substance Act states that consideration to control a drug includes such factors as its actual or relative potential for abuse; the state of current scientific knowledge regarding the drug; its history and current pattern of abuse; the scope, duration, and significance of abuse; what, if any risk there is to the public health.[xxv] These factors have been shown given the current data regarding both the prevalence of recreational use of Viagra, as well as its association with new STDs, including HIV transmission.

A Schedule III Drug is defined as

> (a) The drug or other substance has potential for abuse less than the drugs or other substances in schedules I and II. (b) The drug or other substance has a currently accepted medical use in treatment in the United States. (c) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.[xxvi]

This definition seems to fit the current abuse of Viagra. Classifying Viagra as a Schedule III drug would effectively target the current problems surrounding the drug with recreational use and illegal trading. Though more information is needed, the Drug Enforcement Administration (DEA) or the Department of Health and Human Services (HHS) should schedule proceedings to assess the justifications of controlling Viagra as a Schedule III drug.

**C. Environmental Impact Statement**

Nothing requested in this petition will have an impact on the environment.

**D. Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

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Deputy Health Officer
Director
STD Prevention and Control Services
City and County of San Francisco

Sean Swearingen
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STD Prevention and Control Services
City and County of San Francisco

NOTE: Please see Appendix for Current Letters of Support

## Endnotes


[i] Forbes Magazine, Internet. http://www.forbes.com/home/2003/12/03/cx_mh_1203cialisintro.html

[ii] Kim AA, Kent CK, and Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. *AIDS* 2002, 16:1425-8.

[iii] The President's Council on Bioethics. Beyond Therapy: Biotechnology and Pursuit of Happiness. 2003, pg 104.

[iv] Groseclose S, et al. Summary of Notifiable Diseases—United States. CDC: *Morbidity and Mortality Weekly* 2004, 51(53):1-84.

[v] Increases in HIV Diagnoses—29 States, 1999-2002. CDC: *Morbidity and Mortality Weekly* 2003, 52(47): 1145-1148.

[vi] Kim AA, Kent CK, and Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. *AIDS* 2002, 16:1425-8.

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[viii] Chu PL, McFarland W, Gibson S, Weide D, Henne J, Miller P, Partridge T, Schwarcz S. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *Journal of Acquired Immune Deficiency Syndrome* 2003, 33:191-3.

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[xiii] Brewer DD, Golden MR, Handsfield HH. Factors associated with potential exposure to and transmission of HIV in a probability sample of men who have sex with men. *In* 2004 National STD Prevention Conference; March 8-11, 2004; Philadelphia, PA; pg A.73.

[xiv] Chiliade P, Brown AS, Steinfeld R, Bautista J. Predictors of high risk behavior at a gay men's clinic. *In* 2004 National STD Prevention Conference; March 8-11, 2004; Philadelphia, PA; pg A.167.

[xv] Paniagua F. Commentary on the possibility that Viagra may contribute to transmission of HIV and other sexual diseases among older adults. *Psychological Reports* 1999, 85:942-944.

[xvi] Chu PL, McFarland W, Gibson S, Weide D, Henne J, Miller P, Partridge T, Schwarcz S. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *Journal of Acquired Immune Deficiency Syndrome* 2003, 33:191-3.

[xvii] Kim AA, Kent CK, and Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. *AIDS* 2002, 16:1425-8.

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[xxii] "The New Young Face of Viagra Abuse." *The Chicago Tribune*, December 27, 2003.
[xxiii] Eysenbach G. Online prescriptions of pharmaceuticals: Where is the evidence for harm or for benefit? A call for papers-and for reflection. *Journals of Medical Internet Research* 2001, 3(1):e1.
[xxiv] United States Code of Federal Regulation: 21 C.F.R. § 201.128 (2003).
[xxv] Federal Controlled Substances Act. United States Code of Federal Regulation: 21 C.F.R. § Section 811 (1996).
[xxvi] Federal Controlled Substances Act. United States Code of Federal Regulation: 21 C.F.R. § Section 812 (1996).

**Appendix:** Letters of Support for "Petition to the Food and Drug Administration to change the labeling and take further action to address the association of Viagra (Sildenafil) use and increased STD transmission, including HIV infection"

- AIDS Health Project
  James W. Dilley, MD
  Executive Director

- National Coalition of STD Directors
  Theresa Raphael, MPH
  Executive Director

- American Academy of HIV Medicine
  John Stansell, MD
  Chair, Board of Directors

- California STD Controllers Association
  Jeffrey D. Klausner, MD, MPH
  President

- Northern California Association of HIV Over Fifty
  Monica Dea, MS, MPH
  Director

- Frank Romanelli, Pharm. D., BCPS
  Associate Professor of Pharmacy
  Clinical Pharmacy Specialist in HIV
  University of Kentucky