



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Sidney Wolfe, M.D.
Michael Carome, M.D.
Public Citizen
1600 20th St. NW
Washington, DC 20009

RE: FDA-2014-P-0258

Dear Drs. Wolfe and Carome:

This letter responds to your citizen petition received on February 25, 2014 (Petition). You request that the U.S. Food and Drug Administration (FDA or the Agency):

- (1) add a "black box" warning about the increased risks of heart attacks and other cardiovascular dangers to the product labels of all testosterone-containing drugs presently on the market in the United States;
- (2) ask manufacturers to send "Dear Doctor" letters to warn physicians of these serious adverse effects;
- (3) require that the FDA-approved Medication Guide for testosterone products, dispensed to patients when their prescriptions are filled, be updated to include this new warning; and
- (4) delay the Agency's decision date on approving a new, long-acting, injectable testosterone product Aveed (testosterone undecanoate, Endo) because its approval, absent the new black box warning, would cause further cardiovascular harm to patients for whom this new formulation is prescribed.^{1,2}

¹ On March 5, 2014, FDA approved Aveed (testosterone undecanoate) injection for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, primary hypogonadism (congenital or acquired), or hypogonadotropic hypogonadism (congenital or acquired). The general safety profile of Aveed is comparable to other approved injectable testosterone-containing drugs, with the exception of serious post-injection reactions, and Aveed offered a benefit over currently approved injectable testosterone-containing drugs because it requires considerably fewer injections. For the reasons discussed in this response, the Agency did not believe a delay in Aveed's approval was appropriate based on the evidence submitted in the Petition. You acknowledged the approval in a separate letter to Commissioner Margaret Hamburg dated March 6, 2014. In your letter, you requested that FDA "provide, as quickly as possible, all FDA staff documents concerning the cardiovascular safety of testosterone products, including any documents discussing concerns about these risks in the context of the decision to approve Aveed." Your request for these records, which you subsequently submitted under the Freedom of Information Act (FOIA) on March 11, 2014, will be processed as a FOIA request (FOI 2014-1986).

FDA has considered the information submitted in the Petition, comments to the docket, and other relevant data and information. Based on our review of this information, and for the reasons described below, the Petition is denied.

I. BACKGROUND

A. Testosterone Therapy

Testosterone has been approved or used as a drug in the United States since the 1940s, primarily to stimulate puberty and for the treatment of primary hypogonadism and hypogonadotropic hypogonadism (congenital or acquired) in males.³ Some formulations have also been approved for the treatment of metastatic breast cancer in females.

Some of the clinical manifestations of low testosterone include low libido, increased body fat mass, osteoporosis, muscle wasting, and weakness. Clinical guidelines recommend making the diagnosis of hypogonadism only in men with consistent signs and symptoms, and confirmed low testosterone levels (<300 nanograms (ng)/deciliter (dL)).⁴ The guidelines also suggest confirmatory testing, additional work-up, and a threshold for starting and monitoring testosterone replacement therapy.

Observational studies have shown that generally low testosterone in men is associated with the worsening of biomarkers of cardiovascular health, such as the progression of atherosclerosis,⁵ high cholesterol, and high blood pressure.⁶ There is a growing body of evidence regarding the association between low baseline testosterone and poor cardiovascular health in men. Some studies have attempted to assess the relationship between low testosterone and adverse clinical outcomes such as myocardial infarction (MI)⁷ and cardiovascular mortality,⁸ but it remains

² Petition at 1-2.

³ The first testosterone product, Oreton Methyl (methyltestosterone), was approved as safe by the Agency on January 6, 1940. The effectiveness of Oreton Methyl for the treatment of eunuchism, eunuchoidism, and male climacteric was confirmed in the *Federal Register* on August 1, 1970 (35 FR 12356).

⁴ Bhasin S, Cunningham GR, Hayes FJ et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536-2559; Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *Int J Clin Pract* 2010;64:682-696.

⁵ Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab* 2002;87:3632-3639; Marin P, Holmang S, Gustafsson C et al. Androgen treatment of abdominally obese men. *Obes Res* 1993;1:245-251; Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol (Oxf)* 2010;73:602-612.

⁶ Jones TH, Arver S, Behre HM et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care* 2011;34:828-837; Haring R, Baumeister SE, Volzke H et al. Prospective inverse associations of sex hormone concentrations in men with biomarkers of inflammation and oxidative stress. *J Androl* 2012;33:944-950.

⁷ Cauley JA, Gutai JP, Kuller LH, Dai WS. Usefulness of sex steroid hormone levels in predicting coronary artery disease in men. *Am J Cardiol* 1987;60:771-777; Basaria S, Coviello AD, Travison TG et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363:109-122; Ho CC, Tong SF, Low WY et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU Int* 2012;110:260-265.

⁸ Khaw KT, Dowsett M, Folkard E et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective

unclear. Randomized controlled trials have shown that testosterone supplementation generally improves some biomarkers of cardiovascular health.⁹

B. Regulatory Framework

1. Contraindications, Warnings and Precautions, and Boxed Warnings

FDA regulations state that the Warnings and Precautions section of prescription drug labeling (including the product's package insert) must describe clinically significant adverse reactions, other potential safety hazards, limitations on use imposed by them, and steps that should be taken if such reactions occur (21 CFR 201.57(c)(6)(i)); see also 21 CFR 201.80(e) and (f)).

FDA's *Guidance for Industry on Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Warnings and Precautions Guidance) describes some factors that FDA may consider in assessing whether there is reasonable evidence of a causal relationship between a drug and an adverse event. These include: “(1) the frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.”¹⁰

Under § 201.57(c)(1), a boxed warning may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury (see also § 201.80(e)). A boxed warning must contain, in uppercase letters, a heading that includes the word “WARNING” and other words that convey the general focus of information in the box (§ 201.57(c)(1)). A boxed warning briefly explains the risk and refers to more detailed information

Population Study. *Circulation* 2007;116:2694-2701; Menke A, Guallar E, Rohrmann S et al. Sex steroid hormone concentrations and risk of death in US men. *Am J Epidemiol* 2010;171:583-592.

⁹ Merza Z, Blumsohn A, Mah PM et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. *Int J Androl* 2006;29:381-391; Svartberg J, Agledahl I, Figenschau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res* 2008;20:378-387; Aversa A, Bruzziches R, Francomano D et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010;7:3495-3503; Marin P, Holmang S, Gustafsson C et al. Androgen treatment of abdominally obese men. *Obes Res* 1993;1:245-251; Svartberg J, Aasebo U, Hjalmsen A, Sundsfjord J, Jorde R. Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. *Respir Med* 2004;98:906-913; Hoyos CM, Yee BJ, Phillips CL, Machan EA, Grunstein RR, Liu PY. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomised placebo-controlled trial. *Eur J Endocrinol* 2012;167:531-541; Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol (Oxf)* 2010;73:602-612.

¹⁰ See *Guidance for Industry on Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011), at 3, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>.

in the “Contraindications” or “Warnings and Precautions” section (§ 201.57(c)(1)). A summary of a boxed warning (with the heading WARNING and other words that are appropriate to identify the subject of the warning) must be included in the Highlights section in a box and in bold type (§§ 201.56(d)(1) and 201.57(a)(4)).

FDA’s Warnings and Precautions Guidance states that a boxed warning ordinarily is used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug, or
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), or
- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 “Approval with restrictions to assure safe use” or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) “Risk Evaluation and Mitigation Strategies” Elements to assure safe use).¹¹

The Warnings and Precautions Guidance also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.¹²

2. Safety Labeling Changes Authority under Section 505(o)(4)

Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to authorize FDA to require holders of approved drug and biological product applications to make safety labeling changes, including changes to Medication Guides, for an approved drug based on new safety information that becomes available after the approval of the drug (section 505(o)(4) of the Act (21 U.S.C. 355(o)(4))). As defined in section 505-1(b)(3), new safety information is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.

¹¹ Warnings and Precautions Guidance at 11.

¹² Warnings and Precautions Guidance at 11.

II. DISCUSSION

As the basis for your requests, you cite four studies that you assert “make it clear that testosterone treatment increases the risks of cardiovascular disease, including heart attacks.”¹³ These four studies are: Basaria et al.,¹⁴ Xu et al.,¹⁵ Vigen et al.,¹⁶ and Finkle et al.¹⁷ You also assert that FDA was reckless in making its January 31, 2014, statement that FDA has not concluded that FDA-approved testosterone treatments increase the risk of stroke, heart attack, or death.¹⁸

FDA has considered the studies submitted in support of your requests, which were all known to the Agency prior to the submission of your Petition, and concludes that, at this time, there is insufficient evidence of a causal link between testosterone therapy and adverse cardiovascular outcomes to support the regulatory actions requested in your Petition. However, prior to the submission of your Petition, the Agency had already initiated its own evaluation of the cardiovascular risks of testosterone therapy. The Agency’s final determination regarding the safety of testosterone therapy, and whether FDA will exercise its authority to require safety labeling changes to the labeling of testosterone-containing drugs, is pending the outcome of that evaluation.

In response to your Petition, the Agency evaluated each study you submitted as evidence of a causal relationship between testosterone therapy and adverse cardiovascular outcomes to support the addition of a boxed warning to the labeling, including the Medication Guides, of all FDA-approved testosterone-containing drugs and to support your request that manufacturers send Dear Doctor letters regarding these risks. The Agency determined that each study had significant limitations. In this section, we will address each study in turn.

Basaria et al.

The Petition first discusses the findings of the July 2010 study by Basaria et al., which, you contend, showed a higher rate (described in the Petition as a “significant five-fold increase”) of adverse cardiovascular events in the testosterone group.¹⁹

The Basaria study was a randomized, placebo-controlled trial that evaluated the efficacy of testosterone gel in approximately 200 elderly men at high risk for cardiovascular disease.²⁰ The Data and Safety Monitoring Board for the study recommended study discontinuation due to an overall imbalance of various cardiovascular-related adverse events (e.g., peripheral edema,

¹³ Petition at 5.

¹⁴ Basaria S, Coviello A, Travison T, Storer T, Farwell W, et al. Adverse events associated with testosterone administration. *The New England Journal of Medicine* 2010; 363: 109-122.

¹⁵ Xu L, Freeman G, Cowling B, and Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled trials. *BMC Medicine* 2013; 11: 108.

¹⁶ Vigen R, O'Donnell O, Barón A, Grunwald G, Maddox T, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *Journal of American Medical Association* 2013; 310:1829-1836.

¹⁷ Finkle WD, Greenland S, Ridgeway GK, et al. Increased risks of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE* 2014; 9(1): e85805. Doi:10.1371/journal.pone.0085805.

¹⁸ Petition at 2.

¹⁹ Petition at 3.

²⁰ S Basaria, et al., Adverse events associated with testosterone administration. *N Engl J Med* 2010; 363:109.

arrhythmias, chest pain, elevated blood pressure, MI, and stroke) between the testosterone and placebo groups.

FDA has been aware of the Basaria study since its initial publication in 2010.²¹ After learning of the premature discontinuation of the Basaria study, FDA evaluated the study under a Tracked Safety Issue (TSI) application, an FDA-generated application created for the purpose of tracking and archiving regulatory activities associated with a significant safety issue related to a marketed prescription or over-the-counter drug.²²

We reviewed the Basaria study and concluded that it had several significant limitations that precluded a definitive assessment of the role of testosterone therapy in the cardiovascular events noted in the study. The majority of the cardiovascular events reported were not major adverse cardiac events (MACE), MI, stroke, and deaths due to stroke or MI, and represented diverse pathophysiology. When we evaluated only the MACE that occurred in the study population, we found only a very small numerical imbalance between the testosterone and placebo groups. There were four occurrences of MACE in the testosterone group and none in the placebo group. In addition, the testosterone and placebo groups were not balanced for cardiovascular risk factors, which could explain the imbalance in MACE between the two groups. Regardless, the imbalance between the groups prevented a meaningful interpretation of drug causality.

It is also questionable whether the study results are applicable to the population for whom testosterone therapy is indicated. The study enrolled only elderly men with a high risk of cardiovascular disease and low-normal testosterone levels. However, the indicated population for testosterone therapy is men of all ages with confirmed hypogonadism. Patients with hypogonadism are administered testosterone as replacement therapy with the intention of restoring serum testosterone to normal levels. Generally, it is unclear if testosterone therapy in elderly men with low-normal testosterone levels is replacement or supplementation therapy.

In addition, in 2010 we performed a literature search to identify other articles relevant to the cardiovascular risks of testosterone. We identified two meta-analyses of randomized, placebo-controlled clinical trials and one systematic qualitative review²³ and the Division of Epidemiology (now known as the Division of Epidemiology II (DEPI II)) in FDA's Center for Drug Evaluation and Research reviewed the studies. DEPI II also performed a qualitative review of the constituent studies of the meta-analyses. Upon completing both its evaluation of the original studies and their constituent studies, DEPI II concluded that the studies did not support

²¹ On p. 2 of the Petition you question why FDA had not reassessed the cardiovascular safety of testosterone in light of several studies published in advance of FDA's January 2014 drug safety communication. To be clear, in response to the Basaria study, FDA undertook a clinical and statistical assessment of the cardiovascular risks of testosterone therapy in 2010. The 2014 Drug Safety Communication announced a continuation of that assessment.

²² See FDA Manual of Policies and Procedures 4121.2,

"Tracking of Significant Safety issues in Marketed Drugs -- Use of the DARRTS Tracked Safety Issues."

²³ Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, et al. Adverse Events Associated With Testosterone Replacement in Middle-Aged and Older Men: A Meta-Analysis of Randomized, Placebo-Controlled Trials. *J Gerontol A Biol Med Sci* 2005;60(11):1451-1457; Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Bolona ER, Sideras K, et al. Testosterone and Cardiovascular Risk in Men: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials. *Mayo Clin Proc* 2007;82(1):29-39; and Gruenewald DA, Matsumoto AM. Testosterone Supplementation Therapy for Older Men: Potential Benefits and Risks. *J Am Geriatr Soc* 2003;51(1):101-115.

an association between testosterone therapy and an increased risk of adverse cardiovascular outcomes.

In response to your Petition, we reviewed the Basaria study again, along with the other studies submitted with the Petition. The Basaria study does appear to show an empirical dose-dependent association between testosterone and cardiovascular risk, but it was non-conclusive because of the small sample size and small number of events reported in the study, as well as the limitations with respect to confirming the events. The authors of this study have explicitly indicated that the differences between the groups in cardiovascular adverse events might have been due to chance alone.²⁴

Xu et al.

The Petition then discusses a meta-analysis by Xu et al. of 27 randomized, placebo-controlled trials. The Petition notes that the “13 drug industry-funded trials collectively failed to show any increase in cardiovascular events in the testosterone subjects, but the 14 non-industry-funded trials collectively showed a significant 2.06-fold increased risk with testosterone. There was a significant difference between the cardiovascular risk results from the industry-funded studies and the clearly positive results from those studies not industry-funded.”²⁵ The authors of the Xu study conclude that testosterone increased the risk of cardiovascular-related events.

The meta-analysis by Xu et al. assessed the risks of cardiovascular events in 2,994 men who received testosterone therapy or placebo for at least 12 weeks during 1986–2012. The authors used fixed effect models to compare the risks between testosterone and placebo based on trial-level data from peer-reviewed published papers. The authors conducted two post-hoc sensitivity analyses, including a subgroup analysis that defined subgroups by funding sources. This subgroup analysis used meta-analysis regression models.

The analysis included 1,733 testosterone therapy patients and 1,261 placebo patients. A total of 180 cardiovascular-related events (CREs) were identified among these patients. The risk of CRE was marginally higher among testosterone patients compared with placebo patients (Odds Ratio (OR), 1.54; 95% confidence interval (CI), 1.1–2.2). However, for trials not funded by the pharmaceutical industry, the risk of CRE was more than double among testosterone patients compared with placebo patients (OR, 2.1; CI, 1.3–3.2), while a non-significant protective effect of testosterone for CRE was observed among industry-funded trials (OR, 0.9; CI, 0.5–1.6).

We evaluated the Xu study as evidence for increased cardiovascular risk associated with the use of testosterone therapy. We identified a number of limitations of the study that call into question its utility as evidence to establish a causal relationship between testosterone therapy and increased cardiovascular risk. One major concern is the heterogeneity of the trials and their suitability for integration. The component trials included in this meta-analysis were heterogeneous in almost all aspects of study design—age of participants, inclusion and exclusion criteria, study duration, drug formulation, and dose. The trials included in the analysis differed

²⁴ See Basaria, p. 118. “The cardiovascular adverse events reported in the TOM trial were diverse and may have variable clinical importance. The lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone.”

²⁵ Petition at 3.

in terms of duration of exposure (13 weeks–3 years), year of study (1986–2012), location (10 countries), route of administration of testosterone therapy, formulation of testosterone therapy, and dose of testosterone therapy. The trials also varied widely with regard to their inclusion criteria for hypogonadism, baseline testosterone levels, and the baseline health status of participants, with some trials specifically including certain comorbidities (e.g. rheumatoid arthritis, end-stage renal disease, metabolic syndrome) and some including only healthy individuals. Moreover, the trials differed markedly in the baseline cardiovascular risk of participants.

Another concern was the broad outcome definition used in the Xu meta-analysis. Xu et al. defined the primary safety outcome as “composite cardiovascular–related events” because they anticipated too few events for a robust assessment by cardiovascular event type. Just as in clinical trials, however, a composite outcome in a meta-analysis must be interpretable and appropriate. The composite outcome measure used here included more than 20 categories of cardiac and vascular events, ranging from bleeding esophageal varices, pericarditis, peripheral edema, aortic aneurysm, hypotension, and syncope to events such as death from MI, giving each equal weight. While combining these clinically heterogeneous events with widely varying severity and biological mechanisms may provide the necessary power to detect a difference between treatment arms, the aggregated outcome is difficult to interpret and may mask or distort the signal for the most clinically important cardiovascular outcomes. The authors did perform a secondary analysis that was restricted to serious events and found similar results. However, even this subset was clinically heterogeneous, including such events as “death from bleeding esophageal varices,” “constrictive pericarditis,” and “early elective coronary angioplasty,” while excluding “cardiac disorders not involving death.” The limited interpretability of such broad composite outcomes is one reason that FDA typically uses MACE to assess cardiovascular risks.

Safety outcome ascertainment and incomplete reporting is another major concern with the Xu meta-analysis. Reporting of adverse events in published trials has been shown to vary widely, and a substantial proportion of published trials exclude adverse event information entirely.²⁶ The reported incidence of CREs in the Xu meta-analysis component studies ranged from <1% to 45%, likely reflecting both heterogeneity in study design factors and variable adverse event ascertainment and reporting. Although Xu et al. do not specify the exact number of trials excluded for incomplete adverse event reporting, they note that 138 out of 169 potentially relevant studies (82%) were excluded for “no cardiovascular-related events reported by study arm.” Seven additional studies were either excluded altogether or only a subset of the study’s cardiovascular outcomes were included because of incomplete or conflicting information, despite attempts to contact the study authors. For example, Kaufman et al., one of the larger studies included in the meta-analysis, reported in the text a total of 19 CREs, 17 in the treatment arm, and two in the placebo arm.²⁷ However, Xu et al. included only 11 “vascular disorders” reported in the paper’s adverse event table. Inclusion of CREs in the seven excluded (or partially excluded) studies could potentially add almost 40 additional CREs to the analysis, which could substantially affect the summary estimate.

²⁶ Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. *Arch Intern Med* 2009;169(19):1737-1739.

²⁷ Kaufman J. M. Miller M. G. Garwin J. L. Fitzpatrick S. McWhirter C. Brennan J. J. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med* 2011, 8:2079–2089.

Almost none of the component articles pre-specified cardiovascular safety outcomes, and only two of the included trials attempted to verify events via hospital records. Among the included studies, a substantial portion reported only study withdrawals and it is unclear whether other cardiovascular events—including the types of events reported in other studies and the meta-analysis—may have occurred in these studies. There were additional inconsistencies in component article authors' approaches to recording the number of CREs. For some trials, they reported the number of CREs that occurred and for other trials they reported the number of patients who experienced a CRE. Fifteen of the included trials reported the number of patients who experienced a CRE; seven trials reported the total number of CREs experienced; and five trials reported both the number of CREs and the number of patients who experienced a CRE. In trials that reported the number of CREs, they were not tied to individual patients, so it is possible that one patient experienced multiple CREs. And, even though some of the reported CREs were not tied to an individual patient, the authors used the total number of patients as the denominator in their analysis. Combined with the overly broad definition of CRE and concerns regarding incomplete ascertainment and reporting of safety events, this lack of precision in counting CREs further calls the results into question.

Xu et al. excluded trials under 12 weeks' duration "to assess long-term rather than acute effects of testosterone therapy," but the authors do not specify how many trials were excluded for this reason or how many CREs occurred in these trials.²⁸ It is questionable whether excluding trials of shorter duration was appropriate in this meta-analysis, where excluding a subset of adverse events occurring early in treatment could affect results in an unpredictable manner.

Cardiovascular effects of testosterone may vary across treatment time. Shorter trials may be less vulnerable to certain biases, such as discontinuation and loss to follow up, that could arise in longer studies. It is possible that systematically excluding adverse events that occur early in treatment could create bias.

There were also a number of methodological issues pertaining to the design and conduct of the individual component studies:

- While all included studies were randomized, placebo-controlled trials, a substantial portion were pilot studies or trials with very small sample sizes, and a number of trials had study arm imbalances in baseline cardiovascular risk factors and pre-existing cardiovascular disease. Because many of the studies provided minimal information on baseline cardiovascular risk factors, particularly tobacco use, it was impossible to determine whether there was an imbalance in these risk factors, particularly in the smaller trials.
- The majority of the studies did not specify whether the assessor of cardiovascular-related events was blinded to study drug. Moreover, testosterone therapy can produce noticeable changes in appearance, potentially unmasking both participants and clinicians to study drug and creating bias with respect to patient reporting or clinician assessment of adverse events. The lack of pre-specified, blinded, and systematic collection of CREs may have increased the risk of ascertainment bias.

²⁸ See Xu, p. 2.

- Studies varied widely in their discontinuation rates. Many discontinuations were, because of elevated prostate specific antigens and hematocrits, events more likely to occur in the treatment arm. Such a differential study discontinuation rate would be expected to bias the results toward the authors' conclusions, although it is difficult to predict with certainty the overall effect of study dropouts.

Regarding the discrepancy in testosterone-associated risk found between industry-funded and non-industry-funded trials, this was not a pre-specified analysis and may have been the result of chance.²⁹ This finding could also result from a combination of factors, including differences in adverse event reporting, trial duration, baseline cardiac risk of study participants, discontinuation rates, and drug formulation and dose. A number of differences are apparent between industry-funded and non-industry-funded studies, as grouped by Xu et al; however, how the authors defined the funding source was not clear. Five of the fourteen trials not funded by industry reported using medication given by pharmaceutical companies and eight of the non-industry funded trials either did not provide clear information on funding source or described industry consultancies or other industry ties.

Mean study duration was longer for non-industry funded studies (as defined by Xu et al.). Non-industry funded studies also included participants who were, on average, older and appeared to have a higher prevalence of pre-existing cardiovascular disease and baseline cardiovascular risk factors (based on information provided in the published component studies, which was often incomplete). While these differences should affect the incidence of CREs in both the treatment and placebo arms, it is also possible that they may be due to the differences in age or baseline cardiovascular risk. There was, however, also some suggestion of differential reporting of adverse events. Of the 13 industry-funded studies, five appeared to report only events that resulted in study withdrawal, while only one of the non-industry funded studies reported only those events that resulted in study withdrawal.

Vigen et al.

The Petition then cites a November 2013 study by Vigen et al. discussing the authors' conclusion that "among a cohort of men in the VA [Veterans Affairs] health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes."³⁰ Of note, after the original publication of the study, the investigators received a number of critical comments, which resulted in the issuance of corrections to the initial study. In our evaluation, we reviewed the original paper, the subsequent comments from several research groups, the authors' response, and the authors' correction. The results presented here are obtained from the corrected study report.³¹

²⁹ Protocol: Testosterone and cardiovascular related events in men: a meta-analysis of randomized controlled trials. 12-5-2011. http://www.crd.york.ac.uk/PROSPEROFILES/1815_PROTOCOL_20111108.pdf.

³⁰ Petition at 4.

³¹ Incorrect Number of Excluded Patients Reported in the Text and Figure. *Journal of American Medical Association* 2014, 311: 967. (Incorrect Number); Comment and Response. *Journal of American Medical Association* 2014, 311: 964-965. (Comment and Response).

Vigen et al. conducted a retrospective cohort study to assess the association between testosterone therapy and all-cause mortality, MI, and stroke in men with low testosterone levels (<300 ng/dL) who had undergone coronary angiography between the years 2005 and 2011. The criteria for coronary artery disease as described in this publication was $\geq 20\%$ lesion in any epicardial artery. Of 23,173 candidates assessed, a total of 8,709 men were evaluated (1,223 receiving testosterone and 7,486 not receiving testosterone). The average follow-up was about 840 days (540 days for the testosterone group versus 889 days for the no-testosterone group). Among the 14,464 men excluded, 128 were excluded because they sustained an MI or stroke prior to being prescribed testosterone.

There were a total of 1,710 events (testosterone group: 67 deaths, 23 MIs, 33 strokes; no-testosterone group: 681 deaths, 420 MIs, 486 strokes). For each event, the percentage of occurrence was consistently lower in the testosterone group versus the no-testosterone group, respectively (death: 5.5% versus 9.1%; MI: 1.9% versus 5.6%; stroke: 2.7% versus 6.5%). The authors determined that the association between testosterone and MI, stroke, and death was significant (hazard ratio (HR) 1.29; 95% CI 1.04-1.58) when testosterone therapy was evaluated in an adjusted Cox proportional hazards model with stabilized inverse probability of treatment weighting and treating testosterone as a time varying covariate. The variables used to create the weights were a long list of demographics, concomitant disease, and procedures. After these adjustments, the incidences of death, stroke, and MI were numerically higher in the testosterone group versus the no-testosterone group, but were not statistically significant. Further, the effect of testosterone on cardiovascular risk was harmful in the adjusted analysis (incidence rates: 25.7% for testosterone vs. 19.9% for no-testosterone), but was beneficial in the unadjusted analysis (incidence rates: 10.0% for testosterone vs. 21.1% for no-testosterone).

The strengths of the Vigen study are the size of the database and the linkage to lab results. The study used the nationwide Veterans Affairs system and thus had a large sample size of middle-aged and older men (the mean age for the testosterone group was 61 and was 64 for the no-testosterone group). However, the study was the source of some controversy in the academic community and the authors have acknowledged some key weaknesses associated with this study, including unknown time of day in which blood levels were drawn for testosterone measurement and lack of endpoint validation due to the retrospective nature of the study. FDA also identified a number of limitations with the study.

To start, the Vigen study did require patients to have a low serum testosterone to qualify for inclusion. However, the adequacy of testosterone treatment received is questionable. Only 60% of study patients had a follow-up serum testosterone level evaluated after starting testosterone therapy. On average, the subjects had a baseline testosterone level of 175.5 ng/dL and post treatment level of 332.2 ng/dL, which, while technically within the normal range, is below the target range generally used for treatment (400–500 ng/dL).³² Also, with an average of 332 ng/dL, a substantial number of patients in this study were likely to have had values below the lower limit of normal (300 ng/dL) and to have remained hypogonadal. This is understandable as 63% of study subjects used testosterone patches, a dosage form which often results in

³² The Endocrine Society Clinical Practice guidelines recommend raising serum levels to between 400 and 700 ng/dL. See Bhasin S, Cunningham GR, Hayes FJ et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536-2559.

testosterone levels in the low normal range. The adequacy of testosterone treatment seen in this study does not appear to reflect the recommended clinical guidelines for testosterone replacement. Due to these treatment uncertainties, it is difficult to attribute the increased risk for the composite outcome to testosterone therapy alone. It is important to consider that the study subjects might have simply remained hypogonadal and thus at higher risk for cardiovascular events, regardless of treatment.

The Vigen study also did not include any information on why some patients with low testosterone were treated and others were not treated. Overall, the study population had a high comorbidity burden; however, patients treated with testosterone tended to be younger, have lower testosterone levels, be more overweight, and, generally, have a lower comorbidity burden compared to the no-testosterone group. The criteria for coronary artery disease lacked clinical correlation and relied solely on a subjective angiographic measurement. These selection criteria likely created a cohort of widely variable clinical presentation which may not have been equitably distributed between the arms of the study. Although Vigen et al. used weights to adjust for these imbalances, the two cohorts may not have been balanced with respect to underlying cardiac risk potential, and differences in cardiac outcomes may be due to this imbalance.

In addition, the use of a composite outcome makes the interpretation of the study results less clear. Despite the data showing no significant difference between the testosterone and no-testosterone groups in the incidence of MI, stroke, and death, the authors' conclusions were contradictory to the crude event rates and were based on a complex statistical model using a weighting scheme involving approximately 50 variables. At least one key variable was not accounted for: the significantly lower baseline testosterone level in the testosterone group, which was viewed by the authors' peers as a significant oversight.³³

Finally, the exclusion of 128 patients who experienced MI or stroke before initiating testosterone was not appropriate. These patients should have been included in the analysis and their events included in the no-testosterone group, which would have raised the event rate in the no-testosterone group by 71%. Their exclusion biased the results by reducing the number of events in the no-testosterone group. This issue was also raised by other researchers in their comments regarding this article.³⁴ The authors issued a correction stating that, while their original publication noted that 1,132 patients had been excluded, this was "an incorrect notation" and only 128 patients were excluded for having an MI before testosterone therapy was initiated.³⁵ Although the authors claimed that including the 128 patients did not change the result (HR 1.3; 95% CI 1.1-1.6), their exclusion raises significant concerns about the quality of the study. It is also unclear why the authors excluded 1,301 participants for not having coronary anatomy data (CAD status), considering the wealth of baseline information collected on medical and drug history. It is unclear how this exclusion might also have affected the risk estimate.

Given the described limitations of the study by Vigen et al. it is difficult to attribute the reported findings to testosterone treatment.

³³ Traish, A, et al., 2014, Death by testosterone? We think not! *J Sex Med*, 11:624-629.

³⁴ Comment and Response, 2014.

³⁵ Incorrect Number, 2014.

Finkle et al.

Finally, the Petition relies on the outcome of a 2014 study by Finkle et al. The Petition claims that “the statistically significant findings were that the risk of heart attacks after using the drug [testosterone] for three months was twice the risk in the year before use in all men 65 and over. Furthermore, the study found for the first time that in those men under 65 with a history of heart disease, there was 2.9-fold increase in heart attack risk.”³⁶

Finkle conducted a retrospective cohort study to assess a possible association between testosterone therapy and non-fatal MI 90 days following an initial prescription. The Finkle study had the largest sample size of the four studies reviewed. Finkle used the MarketScan database to identify 55,593 patients prescribed testosterone and 167,279 patients prescribed a phosphodiesterase-5 inhibitor (PDE5I). The authors first used a self-control cohort method to compare the post-exposure incidence rate with the pre-exposure rate among the testosterone exposed cohort, and then used a parallel cohort method to compare the incidence rates between testosterone and PDE5I patients. The results from the self-control analysis showed that for 55,593 patients initiating testosterone, there was a significant increased risk within the first 90 days following initiation of testosterone compared with the risk in one year preceding testosterone therapy (relative risk (RR) 1.36; 95% CI 1.03, 1.81). The subgroup analysis of age and history of heart disease in the testosterone patients also showed significant increased risks for post- versus pre-exposure for participants older than 65 years of age with no heart disease (RR 2.21; 95% CI 1.09-4.46), and less than 65 years of age with heart disease (RR 2.90; 95% CI 1.49-5.62). The results from the parallel cohort analysis were similar. Males in the testosterone cohort had an increased risk for non-fatal MI, ratio of the rate ratios (RRR) (1.27; 95% CI 0.94-1.71). There was an approximate doubling of the risk for males older than 65-years old with heart disease (RRR 1.90; 95% CI 0.66-5.50) and without heart disease (RRR 2.41; 95% CI 1.12-5.17), and for males younger than 65-years old with heart disease (RRR 2.07; 95% CI 1.05-4.11).

These data suggested a significant risk of MI in all patients prescribed testosterone, driven by those patients more than 65 years of age and those patients less than 65 years of age with a history of heart disease. For those patients older than 65 years of age with a history of heart disease taking testosterone, there was no significant risk for MI. Despite these results, the study has some limitations that raise questions about whether there is a true risk for non-fatal MI with testosterone therapy.

The large size of the MarketScan administrative database allowed the investigators to evaluate the risk among a large number of patients. However, in these data, the diagnostic indications for testosterone were not available. Further, results of laboratory testing of testosterone levels are not available; this may be important as low serum testosterone is a known risk for cardiovascular events. Testosterone exposure was determined based on a patient’s filling of a prescription for testosterone therapy, but it is unknown whether the patient actually used the prescription. This fact, combined with the inability to assess baseline or post-treatment testosterone levels or indication for therapy associated with the males treated with testosterone, makes it impossible to determine if the testosterone levels in these treated males had reached therapeutic range. Due to

³⁶ Petition at 5.

these limitations, it is difficult to completely attribute the increased risk for non-fatal MI to testosterone treatment.

It is also questionable as to whether the self-controlled cohort or the active comparator design is most appropriate for assessing outcomes of testosterone therapy. Normally, testosterone is prescribed for chronic use, but Finkle limited follow-up to 3-months of therapy. It is unclear if 3-months' follow-up is adequate to capture the relevant outcomes.

In the testosterone cohort, the males tended to be younger with a higher comorbidity load compared with males in the PDE5I cohort. For both the crossover analyses and the active comparator analysis, the overall risk was small. However, age and heart disease status appear to be confounding factors. In both the crossover and active comparator analyses, the authors found a 2-fold increased risk in males over 65-years old without heart disease and a 2-3 fold increased risk in males with heart disease regardless of age.

In addition, acute non-fatal MI was the only outcome measured. The study subject would have had to survive to be included in the analysis. As fatal MI and other outcomes such as cardiovascular mortality or stroke were not captured, it is unclear how their inclusion would have affected the study results.

Due to these uncertainties, it is difficult to attribute the increased risk for non-fatal MI seen in the Finkle study to testosterone alone and not consider that the study participants might have remained hypogonadic and thus at higher risk for non-fatal MI.

Other Literature

In addition to reviewing the studies cited in the Petition and the literature search discussed above, FDA also performed a literature search to identify other articles that may be relevant to the question of whether testosterone can be linked to increased cardiovascular risk. We identified two relevant studies, which show either an apparent benefit of treatment with testosterone or an inference that testosterone therapy is not associated with an increased cardiovascular risk. The first, a 2012 study by Shores et al.,³⁷ is an observational study designed to examine the association between testosterone treatment and mortality in men with low testosterone. The database included seven Northwest Veterans Affairs medical centers and included a cohort of 1,031 male veterans older than 40 years of age with low testosterone (<250ng/dL). In this study, testosterone treatment was associated with a decreased mortality compared with no testosterone treatment (HR 0.61; 95% CI 0.42-0.88).

Similarly, in a 2013 prospective follow-up from a previously reported cohort that collected data from outpatient medical facilities with access to medical records, Muraleedharan et al.³⁸ concluded that low testosterone levels predicted an increase in all-cause mortality during long-term follow-up, and testosterone replacement may improve survival in hypogonadal men with type 2 Diabetes Mellitus.

³⁷ Shores, M, et al., 2012, Testosterone treatment and mortality in men with low testosterone levels, *J Clinical Endocrinol Metab*, 97 (6):2050-2058.

³⁸ Muraleedharan, V, et al., 2013, Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes, *Eur J Endocrinol*, 169: 725-733.

The Shores study used a lower threshold for low testosterone (<250 ng/dL) to increase the likelihood of a symptomatic hypogonadal population. In both studies, lower testosterone level was associated with testosterone therapy, but Body Mass Index and younger age were also predictors of use of testosterone in the Shores study. Otherwise, comorbid conditions were balanced between the cohorts in each of the studies. Both studies used time-to-event Cox regression analysis to calculate the risk estimates and confidence intervals, and they each showed an approximate 50% reduction in the risk for death with testosterone therapy.

In addition, the Shores study showed that increasing mortality is associated with lower baseline testosterone levels and shorter duration of testosterone therapy. This might indicate that sicker, undertreated males are at a higher risk for mortality. The Muraleedharan study showed a similar mortality rate for the diabetic males on testosterone and for a cohort of diabetic males who had normal testosterone levels and no testosterone therapy, which suggests the untreated males in this study have similar outcomes to the treated hypogonadal males. On average, duration of testosterone therapy was longer than two years for the majority of the treated subjects, and the peak testosterone level was 657 ng/dL. Over 67% of the treated males had a testosterone level of over 518 ng/dL. These levels are well within the recommended mid-to-normal therapeutic levels (400 – 700 ng/dL). In both studies, only all-cause mortality was reported as the outcome, so outcomes of interest that did not result in death were not captured.

FDA's Response

As discussed in this response, the studies presented in the Petition have significant limitations that weaken their evidentiary value for confirming a causal relationship between testosterone and adverse cardiovascular outcomes. These weaknesses include:

- Short follow-up times precluding assessment of the potential for long term benefits of testosterone therapy (Finkle);
- Unclear statistical methods (Vigen);
- Inability to compare results across studies due to differing outcomes and populations (Vigen, Finkle);
- Overall effect estimates are small and may be due, in part, to residual confounding (Vigen, Xu, Finkle);
- Limitations with respect to ascertainment of events (Basaria, Finkle);
- Overly broad case definition for cardiovascular events (Xu);
- Incomplete or unavailable laboratory data to confirm hypogonadism or to assess whether patients returned to normal testosterone levels after receiving treatment (Finkle, Vigen);
- Failure or inability to assess other potentially relevant laboratory data such as hematocrit or hemoglobin (Finkle);
- Non-validated endpoints or lack of compliance data (Finkle, Vigen, Xu); and
- Conflicted results suggesting both a testosterone benefit (Shores and Muraleedharan) and testosterone harm with respect to cardiovascular risk, or no difference between groups (Vigen, Xu).

In addition, FDA has identified other studies in the literature that contradict the findings in the studies submitted.

Prior to the submission of the Petition, the Agency had already undertaken a thorough evaluation of the literature and other evidence to determine if additional regulatory action is necessary to protect consumers from the cardiovascular risks of testosterone therapy. As our January 31, 2014, drug safety communication indicated, FDA believes that the publication of these studies warrants further exploration of a possible safety signal regarding testosterone and cardiovascular risk. Our current evaluation remains ongoing. For the reasons discussed above, the Agency does not believe at this time that the evidence presented in the Petition is sufficient to require the addition of a boxed warning regarding cardiovascular risks of testosterone therapy to the labeling of all testosterone products. Therefore, at this time, FDA declines to exercise its authority to require safety labeling changes regarding these risks on the basis of the evidence presented in the Petition, and your request is denied. Consequently, your requests that FDA require FDA-approved Medication Guides for testosterone products to be updated with the same warnings and that manufacturers be required to send Dear Doctor Letters regarding these risks are also denied.

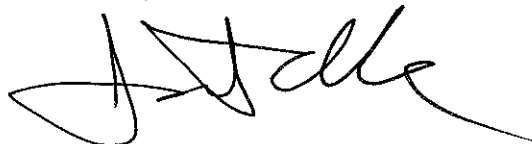
We are continuing to assess this potential safety signal. In particular, we are awaiting the results of the Testosterone Trial,³⁹ a multicenter study of six coordinated trials investigating the effects of testosterone treatment in elderly men with low testosterone on physical function, vitality, sexual function, cognitive function, anemia, and cardiovascular risk. Eight hundred men over 65-years-of age whose serum testosterone is less than 250 ng/dL have been or will be randomized to receive testosterone or placebo double blindly for one year. Although this trial is not a safety study, we believe that the data will yield important information regarding the safety of testosterone with regard to cardiovascular risks. In addition, we intend to present the question of the potential association between testosterone and adverse cardiovascular events to an Advisory Committee this fall.

Based on the outcome of these efforts, FDA intends to make a determination as to whether any regulatory action is warranted, such as invoking our authority to require safety labeling changes under section 505(o)(4) of the FD&C Act for testosterone-containing drugs, as appropriate.

III. CONCLUSION

After careful consideration, and, in light of the foregoing, we hereby deny your Petition in its entirety. FDA will continue to evaluate the cardiovascular risks of testosterone, and, if warranted, will take appropriate regulatory action to protect the public health when its evaluation has concluded.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', with a large, stylized flourish extending to the right.

Janet Woodcock, M.D.
Director

Center for Drug Evaluation and Research

³⁹ For more information regarding the Testosterone Trial, see <http://www.med.upenn.edu/edom/t-trial.html>.