Open Letter to the FDA Concerning the 1/31/2014 Safety Announcement entitled:
FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products

As concerned physicians and scientists, we must be mindful of false positives, false negatives, poor study design, selection bias, failure to adequately address confounding conditions, statistical manipulation, and, most importantly, improperly drawn causal inference – all of which can result in a false conclusion being published. The Economist magazine review on this topic (October 19th, 2013 edition – "Problems with Scientific Research") cites the independent findings from multiple distinguished institutions that less than 25% of scientific published studies are in fact reproducible. Unfortunately, while there is much yet to be learned about testosterone therapy, the two studies cited by the FDA (due in part to the headline grabbing nature of their titles) are of very inferior quality.

Poor quality medical articles such as these have the potential to create significant population health risks, as often has happened in the past. For example, an article published in 1941 by Drs. Huggins and Hodges purported to prove that testosterone caused prostate cancer genesis and growth, with much of their conclusions based upon only one patient. This led to 60 years of castration and androgen deprivation therapy in men unfortunate enough to be diagnosed with prostate cancer. These treatments caused decades of untold suffering due to the morbidity and mortality of the "cures". The 1941 "study" by Huggins et al was false and invalid from the start; and its conclusions were close to the opposite of the truth. Seventy years later, we now know from validated biochemical research that the testosterone-albumin complex initiates prostate cell apoptosis, thus giving us a possible avenue for cure. So as to avoid repeating similar travesties of the past, this peer reviewed letter is being sent to the FDA with the hope that we will not focus on the headline grabbing false conclusions of the two studies cited with anything but skepticism.

The FDA Safety Announcement cites two articles that were terminally flawed and made conclusions that run counter to vast numbers of scientific articles on testosterone from the past 20 years. The JAMA study, entitled "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels" was a retrospective chart review of men with low testosterone levels who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011. Oddly, the study's findings as presented in the Results section of the Abstract are completely counter to the article's Conclusion. The Results section states that of the 1223 men who received some form of testosterone therapy, there was a 5% mortality rate, a 1.8% heart attack rate, and a 2.7% stroke rate. Conversely, of the 7486 men who did not receive testosterone therapy, there was a 9% mortality rate, a 5.6% heart attack rate, and a 6.5% stroke rate. The raw data the authors presented in the Results section of the JAMA article demonstrated that the group that had received some form of testosterone therapy had a 45% **reduction** in mortality, a 68% **reduction** in heart attacks, and a 58% **reduction** in strokes.

Additionally, the low quality JAMA data was gleaned from a retrospective chart review with undocumented testosterone treatment levels from multiple forms of T therapy in the "treatment cohort". Instead of submitting this poor quality data "as is", which would have weakly supported years of better published studies on the benefits of testosterone therapy, the authors choose to use inverse probability treatment weighting to "adjust" for differences in demographics and prior risk factors in order to *theoretically* account for potential confounding variables that might affect the patients' outcome. In this case, they used over 50 variables to compute this weighting and change the data. Strangely, the researchers did not include the use of hypertensive drugs as a possible confounding or mitigating factor affecting the outcome, though hypertension is a leading causative factor in heart attacks and strokes. By selecting the specific statistical variables as they did, it was possible for the authors to change their own data that clearly supported the beneficial effects of even sub-therapeutic levels of testosterone to an opposite conclusion.

The second article cited titled "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men" is equally flawed and perhaps more scientifically outrageous. In this paper, the authors compared the myocardial infarction and mortality rates of men prescribed testosterone for low T versus men prescribed PDE inhibitors such as Cialis™ or Viagra™. The glaring errors in this study include that the authors did not measure or know the testosterone levels of the men in the PDE-I cohort, nor did they measure or know the

baseline or post-treatment T levels in the testosterone treated group. The study extracted the data from a review of insurance submitted prescriptions and post-prescriptions insurance ICD diagnosis codes. In reality, what the authors compared in this paper was a group of men with presumably low testosterone (who may not have received adequate treatment for low T) against an unrelated cohort of men with unknown but presumed average testosterone. Amazingly, this PLOS article did not even measure the one variable they were supposedly studying – testosterone. Clearly, the two groups in this paper are not comparable; and, the study is of no value. If one assumes the men given T prescriptions had "low T", then these authors may have also inadvertently lent support to the more established findings across two decades of studies linking men with low testosterone levels to significantly higher levels of myocardial infarctions and mortality from all causes: the PLOS study's presumed low testosterone group had higher levels of MIs and mortality for the first 3 months of treatment, but not after 3 months of treatment. Unfortunately, it is impossible to draw any conclusion from this paper as the authors did not have scientifically valid comparable cohort groups or critically important patient data.

While much quality prospective, randomized, and double blind (when possible) research still needs to be done on the topic of testosterone supplementation in men and women, the studies that have qualified in this regard have shown dramatic benefits without health risk in men and women when molecularly human identical testosterone was appropriately delivered (compressed steady state release subcutaneous testosterone pellets being the ideal therapy option in my opinion). Furthermore, as the American Journal of Cardiovascular Drugs stated in 2005: "testosterone treatment is reported to reduce serum levels of the pro-inflammatory cytokines interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha, and to increase levels of the anti-inflammatory cytokine IL-10; to reduce vascular cell adhesion molecule (VCAM)-1 expression in aortic endothelial cells; to promote vascular smooth muscle and endothelial cell proliferation; to induce vasodilatation and to improve vascular reactivity, to reduce serum levels of the pro-thrombotic factors plasminogen activator inhibitor (PAI)-1 and fibrinogen; to reduce low-density lipoprotein-cholesterol (LDL-C); to improve insulin sensitivity; and to reduce body mass index and visceral fat mass. These actions of testosterone may confer cardiovascular benefit since testosterone therapy reduces atheroma formation in cholesterol-fed animal models, and reduces myocardial ischemia in men with CHD." It is therefore most difficult to imagine a scenario where this human hormone (unadulterated) would increase cardiovascular risk.

Sincerely,

Mark Richards MD
Rockville, MD