FORMAL COMMENTS TO THE U.S. FOOD AND DRUG ADMINISTRATION

Re: [Docket No. FDA-2025-N-6743] – Scientific and Clinical Considerations for Testosterone Replacement Therapy (TRT) in Men with Hypogonadism

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Organization: Alliance for Pharmacy Compounding and National Community Pharmacists Association

The Alliance for Pharmacy Compounding (APC) and the National Community Pharmacists Association (NCPA) respectfully submit these comments to the U.S. Food and Drug Administration (FDA) in response to the Request for Information (RFI) regarding the Expert Panel on Testosterone Replacement Therapy (TRT). APC and NCPA provide an evidence-based perspective on the clinical necessity, safety profile, and appropriate use of TRT to support the Agency's goal of ensuring patient safety while maintaining access to medically necessary therapies.

I. EXECUTIVE SUMMARY

- Clinical Benefit: TRT in men with confirmed hypogonadism improves sexual function, mood, body composition, and bone health, and shows significant potential in preventing or reversing metabolic disorders like Type 2 Diabetes (T2DM) [1, 4, 11, 12].
- Safety Profile: Large-scale randomized data (TRAVERSE) and updated meta-analyses demonstrate that TRT is not associated with increased major cardiovascular events or high-grade prostate cancer in appropriately screened and monitored populations [2, 13, 16].
- Diagnostic Rigor: APC and NCPA support maintaining a diagnostic threshold of two fasting morning total testosterone levels below 350 ng/dL, accompanied by clinical symptoms, to ensure therapy is reserved for pathological hypogonadism [1, 7, 15].
- Regulatory Recommendation: FDA labeling and communications should distinguish between evidence from monitored, indicated populations and unstudied high-risk groups, while acknowledging emerging evidence for metabolic benefits.

II. NARRATIVE CLINICAL PERSPECTIVE

The risk-benefit profile of TRT is fundamentally tied to patient selection and longitudinal monitoring. For nearly two decades, observational data have linked low testosterone in older men to a 35–40% increase in all-cause mortality [17, 18]. Appropriately prescribed TRT addresses multi-systemic complications of untreated hypogonadism, including osteoporosis and frailty [4, 10].

Recent high-quality evidence, including the TRAVERSE trial, has largely mitigated historical concerns regarding cardiovascular and prostate safety in the indicated population [13, 16]. Furthermore, meta-analyses confirm that TRT does not worsen lower urinary tract symptoms

(LUTS) or BPH-related measures [12]. While TRT is not a primary antidepressant, it provides secondary mood benefits for men with confirmed deficiency [14]. APC and NCPA urge FDA to ensure that labeling reflects this contemporary evidence to support informed clinical decision-making.

III. DETAILED CLINICAL AND SCIENTIFIC CONSIDERATIONS

A. Impact on Health Systems and Patient Care

Appropriate diagnosis and treatment of hypogonadism have implications beyond symptom relief, affecting multiple organ systems and overall health system burden. Published evidence demonstrates that TRT improves bone mineral density and reduces fracture risk in men, who are a population in which osteoporosis is underrecognized and undertreated [4, 10, 16].

For nearly two decades, observational data have shown that lower testosterone levels in older men (mean age >60 years) are associated with higher all-cause mortality (ACM), with approximately a 35–40% increased risk of death in men in the lowest testosterone quartile compared with higher quartiles [1–3]. Restricting access to TRT in appropriately selected men with diagnosed hypogonadism may increase the incidence of preventable comorbidities, including frailty, metabolic syndrome, type 2 diabetes (T2DM), and cardiovascular events [3, 5, 10, 11].

Given the potential for TRT to prevent or mitigate these outcomes in appropriately selected patients, APC and NCPA urge the FDA to consider broader health-system and patient-care implications when evaluating regulatory policies and labeling related to TRT access.

B. Risk–Benefit Profile and Patient Selection

The risk–benefit profile of TRT is highly dependent on appropriate patient selection and ongoing monitoring. Benefits are most pronounced in men with confirmed pathological hypogonadism, for whom TRT has been shown to improve sexual function, mood, body composition, and certain metabolic parameters [1, 4, 8, 9, 11, 16]. Known risks such as erythrocytosis can generally be managed through dose titration, hematocrit monitoring, and, when appropriate, therapeutic phlebotomy [1, 7].

Age and baseline comorbidities, including obesity, prediabetes, and established cardiovascular disease, modulate outcomes. For example, in the T4DM trial, prevention of progression to T2DM was at least partly mediated by reductions in fat mass and improvements in muscle strength [3, 11]. In addition, exogenous testosterone suppresses spermatogenesis and is generally avoided in men actively desiring fertility; counseling and discussion of alternatives are therefore critical in this population [16].

Current evidence, including the large TRAVERSE randomized trial, indicates that appropriately

prescribed TRT for men with confirmed hypogonadism is not associated with increased major cardiovascular risk compared with placebo [2, 4, 16]. Available data suggest that increased venous thromboembolism (VTE) risk, when present, may be confined mostly to men with underlying thrombophilia, underscoring the importance of thorough medical history and risk assessment prior to treatment initiation [16].

Taken together, these findings support a regulatory and labeling framework that emphasizes diagnostic rigor, careful patient selection, and ongoing monitoring to optimize the risk–benefit profile of TRT.

C. Provider and Patient Education

Standardized education for healthcare providers and patients is essential to consistent and appropriate use of TRT. Major guidelines emphasize the need to:

1. Obtain at least two fasting morning total testosterone measurements to establish biochemical hypogonadism [1, 7, 8, 15];
2. Confirm the presence of compatible clinical symptoms and signs (e.g., decreased libido, erectile dysfunction, reduced energy, decreased muscle mass, reduced bone density) alongside biochemical deficiency [1, 7, 8]; and
3. Recognize that TRT aimed at metabolic benefits (e.g., T2DM prevention or remission) often requires long-term therapy and integration with lifestyle interventions [3, 5, 11].

APC and NCPA encourage FDA to ensure that labeling and professional guidance clearly highlight these diagnostic and educational elements, thereby supporting appropriate prescribing and realistic patient expectations regarding timelines and outcomes.

D. Stakeholder Collaboration and Evidence Generation

Collaborative infrastructure can significantly enhance the evidence base. APC and NCPA recommend that the FDA work with professional societies, academic centers, and patient advocacy groups to establish a national TRT outcomes registry. Such a registry would:

- Capture long-term cardiovascular and prostate outcomes;
- Track durability of metabolic improvements (e.g., T2DM remission or prevention); and
- Provide real-world safety and effectiveness data that supplement but do not replace randomized controlled trials [2, 3, 5, 10, 16].

FDA support for such collaborations could enable more nuanced, data-driven regulatory decision-making in the TRT domain.

E. Erectile Function

Erectile dysfunction (ED) is a common and clinically meaningful manifestation of male hypogonadism and should be considered an important patient-centered outcome in assessments of TRT's benefit–risk profile. An updated systematic review and meta-analysis of randomized

controlled trials in late-onset hypogonadism (28 RCTs; ~3,253 participants) reported that TRT was associated with statistically significant improvement in erectile function compared with placebo, as measured by the International Index of Erectile Function (IIEF): weighted mean difference (WMD) +3.26 (95% CI 1.65–4.88; P < 0.0001) [12].

This improvement was observed across multiple administration routes (injection, transdermal, oral) and across treatment durations (<12 months and ≥12 months) [12]. FDA labeling and risk–benefit assessments should recognize erectile function as a meaningful and evidence-supported benefit for appropriately selected men with hypogonadism.

F. Lower Urinary Tract Symptoms (LUTS) and BPH-Related Measures

Concerns about potential worsening of lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) parameters can deter appropriate TRT use. However, the updated systematic review and meta-analysis found no evidence that TRT worsens LUTS or BPH-related objective measures compared with placebo, including [12]:

- International Prostate Symptom Score (IPSS): WMD 0.00 (95% CI –0.45 to 0.45; P = 1.0)
- Prostate volume: WMD 0.38 (95% CI –0.64 to 1.41; P = 0.46)
- Maximum urinary flow rate (Qmax): WMD 1.86 (95% CI –0.98 to 4.69; P = 0.20)
- Post-void residual (PVR): WMD 3.20 (95% CI –5.87 to 12.28; P = 0.49)
- Prostate-specific antigen (PSA): WMD 0.08 (95% CI 0.00 to 0.17; P = 0.06)

Overall, these data indicate that, in studied populations of appropriately selected men, TRT can improve erectile function without statistically significant adverse effects on LUTS/BPH-related measures [12]. APC and NCPA recommend that FDA consider these findings when evaluating whether additional LUTS-related restrictions or warnings are warranted for on-label TRT use.

G. Prostate Cancer and Other Prostate Safety Events

Given longstanding concerns about the safety of prostate treatment, data from large, well-controlled trials are particularly important. The TRAVERSE prostate safety analysis (placebo-controlled, double-blind randomized clinical trial; ~5,200 men ages 45–80) enrolled men with confirmed hypogonadism and excluded those at higher baseline prostate cancer risk (e.g., PSA >3.0 ng/mL, IPSS >19). In this carefully screened population, adjudicated prostate outcomes were low and not significantly different between TRT and placebo arms [13]:

- High-grade prostate cancer (Gleason ≥4+3): HR 1.62 (95% CI 0.39–6.77; P = .51)
- Any prostate cancer: HR 1.07 (95% CI 0.47–2.42; P = .87)
- Acute urinary retention: HR 1.25 (95% CI 0.65–2.41; P = .50)
- Invasive procedure for BPH: HR 1.91 (95% CI 0.95–3.84; P = .07)

The trial also found no differential worsening of LUTS (no significant change in IPSS between groups), whereas PSA increases were modestly greater in the TRT group, with the largest between-group difference observed at approximately 12 months [13].

Other large RCTs and observational studies have similarly found no substantial increase in prostate cancer incidence or high-grade disease with TRT, and some real-world data suggest no increased prostate cancer risk even among men with a family history of prostate cancer [12, 16]. Emerging evidence supports the safety of TRT in carefully selected men with treated, low-risk prostate cancer (e.g., post-prostatectomy or post-radiotherapy), without observed increases in recurrence or biochemical failure in closely monitored settings [16].

These data support the conclusion that, in appropriately selected, screened, and monitored men, TRT is not associated with clinically meaningful increases in prostate cancer or other serious prostate-related outcomes.

H. Monitoring, Patient Selection, and Generalizability

FDA communications and labeling should clearly distinguish:

- Evidence generated in appropriately selected men with confirmed hypogonadism who undergo baseline prostate risk assessment and ongoing monitoring (e.g., TRAVERSE-type populations) [1, 7, 13, 16]; from
- Populations excluded from pivotal trials or meta-analyses, such as men with known prostate cancer, significantly elevated PSA at baseline, or severe LUTS.

TRAVERSE's prostate safety findings, for example, are not necessarily generalizable to men with active or higher-risk prostate cancer or with substantially higher baseline PSA and IPSS scores. At the same time, the evidence summarized above supports the conclusion that, in indicated populations under appropriate monitoring, TRT is not associated with clinically meaningful worsening of LUTS/BPH-related measures, although modest PSA increases can occur and warrant routine surveillance [12, 13].

Thus, baseline screening and longitudinal monitoring (hematocrit, PSA, digital rectal examination, symptom review) are essential components of appropriate TRT use and should be clearly reflected in labeling and professional guidance [1, 7].

I. Depression and Mood Symptoms

Depressive symptoms and reduced mood are common among men with symptomatic hypogonadism. The clinical literature on TRT specifically as a treatment for depression is mixed, with some studies showing benefit in selected subgroups (e.g., men with low testosterone, dysthymia/subthreshold depression, or certain treatment-resistant depression contexts) and others showing no significant difference versus placebo [14].

APC and NCPA agree with the prevailing guideline-based approach that TRT should not be positioned as a primary antidepressant. Instead, TRT should be used for men with confirmed symptomatic hypogonadism according to established criteria; in such patients, improvements in mood and depressive symptoms may occur as secondary benefits in a subset of patients [1, 7, 14].

This framing supports accurate risk–benefit communication, helps prevent off-label or inappropriate use, and preserves access for men who meet recognized diagnostic criteria.

J. Clinical Necessity of Compounded Testosterone Therapy for Certain Men

While FDA-approved testosterone products play an important role in the treatment of hypogonadism, commercially available options do not meet the clinical needs of all men. In real-world practice, a subset of patients requires individualized dosing, alternative routes of administration, or formulation adjustments that cannot be achieved using FDA-approved testosterone products as labeled.

Men may be unable to tolerate commercially available products due to adverse reactions, excipient sensitivities, or inconsistent absorption. Others require dosing increments or concentrations that fall between fixed commercial strengths, particularly when titrating therapy to maintain physiologic testosterone levels while minimizing adverse effects such as erythrocytosis or supraphysiologic peaks. Commercial products are often limited to standardized dosing schedules that do not accommodate individualized pharmacokinetic responses.

In addition, some men require alternative routes of administration that are not adequately addressed by existing FDA-approved options. For example, patients who experience poor absorption or skin reactions with transdermal products, injection-site complications, or fluctuations associated with long-acting injectables may benefit from alternative compounded formulations or delivery methods tailored to their clinical circumstances.

Compounded testosterone preparations, when prescribed for an identified individual patient pursuant to a valid prescription and compounded in compliance with Section 503A of the Federal Food, Drug, and Cosmetic Act and applicable USP standards, serve an important clinical role for men whose medical needs cannot be met by commercially available products. Restricting access to compounding in this context would not enhance patient safety, but instead would leave certain men without a viable therapeutic option for the treatment of clinically confirmed hypogonadism.

APC and NCPA urge FDA to recognize the legitimate and medically necessary role of pharmacy compounding in testosterone replacement therapy for select patients, particularly where FDA-approved products are not clinically appropriate due to dosing limitations, route-of-administration constraints, or patient-specific tolerability issues.

K. Increasing Access to Testosterone Therapy Through Descheduling

Testosterone's current classification as a Schedule III controlled substance creates access barriers that are not aligned with its contemporary clinical use, safety profile, or abuse potential when prescribed appropriately for hypogonadism. While scheduling decisions historically reflected concerns related to non-medical anabolic steroid misuse, those concerns should be distinguished

from the medically supervised treatment of testosterone deficiency in men with confirmed hypogonadism.

Controlled substance designation imposes additional administrative and logistical burdens on prescribers and pharmacies, including heightened prescribing restrictions, storage requirements, dispensing limitations, and monitoring obligations. These barriers can delay or interrupt care for patients with legitimate medical need and disproportionately affect men who require ongoing, carefully titrated therapy under physician supervision.

Importantly, testosterone therapy for hypogonadism does not share the same abuse patterns or public health risks associated with opioids or other controlled substances when used within established diagnostic and monitoring frameworks. Contemporary evidence, including large randomized trials and real-world data, supports the safety of testosterone therapy in appropriately selected and monitored patients, without signals suggesting misuse at the population level comparable to other scheduled drugs.

Descheduling testosterone, or otherwise reevaluating its controlled substance status, could meaningfully improve patient access while preserving appropriate clinical oversight. Removing testosterone from the controlled substance schedules would reduce unnecessary administrative friction, improve continuity of care, and allow clinicians to focus on evidence-based patient selection, dosing, and monitoring rather than compliance with regulatory mechanisms designed for substances with fundamentally different risk profiles.

APC and NCPA encourage FDA to work collaboratively with the Drug Enforcement Administration and other federal stakeholders to reassess testosterone's scheduling status in light of current clinical evidence, real-world use patterns, and the demonstrated medical necessity of long-term testosterone replacement therapy for men with hypogonadism.

IV. SCIENTIFIC CONSIDERATIONS

A. Diagnostic Definitions and Thresholds

APC and NCPA support a diagnostic framework requiring at least two fasting morning total testosterone levels below approximately 350 ng/dL, in combination with consistent clinical symptoms of hypogonadism [1, 7]. Guidelines from the International Society for the Study of the Aging Male a(ISSAM), the European Association of Urology (EAU), the European Society of Endocrinology (ESE), the European Academy of Andrology (EAA), and the American Urological Association (AUA) converge on a total testosterone (TT) range of roughly 250–350 ng/dL as the threshold for low testosterone [1, 7, 15].

For age-related androgen deficiency, APC and NCPA emphasize that although testosterone levels naturally decline with age, the presence of symptomatic hypogonadism in older men justifies consideration of TRT to prevent functional decline and preserve quality of life [1, 9, 16, 19, 20, 21].

Maintaining current diagnostic criteria helps ensure appropriate patient selection and minimizes the risk of treating men without true pathological hypogonadism.

B. Research Priorities and Scientific Gaps

While recent large-scale trials support the cardiovascular non-inferiority of TRT versus placebo among appropriately selected men, important gaps remain, particularly for high-risk subgroups (e.g., men with advanced cardiovascular disease, more severe metabolic dysfunction, or complex comorbidities) [2–4, 11, 16]. Key priorities include:

- Longer-term (>5 years) randomized and observational data on cardiovascular outcomes;
- Better characterization of mechanisms through which TRT influences vascular health, insulin sensitivity, and body composition [3]; and
- More granular data on subpopulations stratified by age, comorbidities, and baseline risk profiles.

FDA could consider whether targeted prospective studies in these high-risk or under-studied subgroups would support more refined labeling, including risk mitigation strategies and patient selection guidance.

C. Scientific Barriers to Evidence Generation

A principal barrier to robust evidence generation in TRT is the limited duration of many existing trials and the challenges of maintaining large cohorts under therapy for multiple years. Many studies have relatively small sample sizes or short follow-up periods, which may under-represent the full spectrum of TRT's potential long-term benefits (e.g., prevention of T2DM, preservation of bone density, reduction in fractures) and risks [4, 5, 10, 11].

FDA could consider whether regulatory incentives, public–private partnerships, or other collaborative mechanisms might encourage sponsors and academic investigators to conduct longer-term studies and maintain well-characterized cohorts.

D. Additional Scientific Tools and Data Sources

Advanced analytical methods, including mediation analysis and counterfactual frameworks, can clarify the pathways by which TRT exerts its clinical effects (for example, the extent to which improvements in metabolic outcomes are mediated by changes in body composition vs. other mechanisms) [3].

Real-world data sources, such as longitudinal registries, large administrative claims datasets, and integrated health system records, can offer complementary insights into long-term safety and effectiveness that are difficult to capture in traditional randomized trials [2–5, 10, 12, 13, 16]. APC and NCPA encourage FDA to recognize real-world evidence as a complement to randomized controlled trials and to consider opportunities to harmonize data elements across registries to maximize its regulatory utility.

E. Potential New Uses and Areas for Evidence

An important emerging area is the use of TRT as part of metabolic intervention strategies for men with hypogonadism and T2DM or prediabetes. Existing evidence suggests that TRT can help prevent progression to T2DM and, in some cases, contribute to partial or complete disease remission when combined with lifestyle interventions and standard metabolic care [3, 5, 11]. Long-term registry data further support sustained improvements in glycemic control and body composition in such men [5].

APC and NCPA urge FDA to consider whether these data, as they continue to mature, might support:

- Labeling modifications or clarifications regarding metabolic effects, and/or
- Carefully framed additional indications or clinical use statements in high-risk men with clearly defined hypogonadism and metabolic comorbidity profiles.

V. RECOMMENDATIONS

Based on the current evidence base and clinical practice guidelines, APC and NCPA respectfully recommend that FDA:

1. Maintain current diagnostic criteria for testosterone deficiency, i.e., at least two fasting morning total testosterone levels below approximately 350 ng/dL together with compatible clinical symptoms and signs, to ensure appropriate patient selection [1, 7, 15];
2. Evaluate whether current labeling adequately reflects contemporary evidence regarding: (a) improvement in erectile function among appropriately selected men; (b) the absence of significant worsening in LUTS/BPH-related measures in studied populations; and (c) prostate cancer and other prostate-related event rates observed in large RCTs and meta-analyses [4, 8, 9, 12, 13, 16];
3. Clearly distinguish in regulatory communications between: (a) evidence from carefully selected, screened, and monitored men with confirmed hypogonadism (e.g., TRAVERSE and similar trials); and (b) populations excluded from pivotal studies (e.g., men with active or high-risk prostate cancer, markedly elevated PSA, or severe LUTS), to avoid inappropriate extrapolation;
4. Support collaborative efforts to establish a national TRT outcomes registry and harmonized real-world data infrastructure to generate long-term safety and effectiveness data, particularly on cardiovascular, prostate, and metabolic outcomes [2–5, 10, 12, 13, 16];
5. Consider whether labeling modifications or clarifications are warranted regarding: (a) metabolic benefits, including potential roles in T2DM prevention and remission in appropriately selected men; and (b) mood symptom improvements as secondary benefits in men with confirmed hypogonadism, while avoiding positioning TRT as a primary treatment for depressive disorders [3, 5, 11, 14];

6. Clarify that TRT is not a first-line antidepressant, while acknowledging that some men with biochemically and clinically confirmed hypogonadism may experience mood and energy improvements as a consequence of restoring physiologic testosterone levels [1, 7, 14];
7. Ensure that baseline prostate risk assessment and ongoing monitoring requirements (e.g., PSA, hematocrit, prostate exam, periodic symptom review) are clearly communicated in labeling and professional guidance, reflecting evidence on PSA changes and prostate safety in indicated populations [1, 7, 12, 13, 16].
8. Ensure that FDA policies, guidance, and communications explicitly recognize the legitimate role of pharmacy compounding under Section 503A for testosterone replacement therapy in patients whose medical needs cannot be met by FDA-approved products alone, including situations involving individualized dosing, alternative routes of administration, or formulation-specific tolerability concerns, as discussed in Section III.J;
9. Encourage interagency collaboration to reevaluate testosterone's classification as a Schedule III controlled substance in light of contemporary clinical evidence, real-world use patterns, and patient access considerations, recognizing that unnecessary scheduling-related barriers may impede appropriate care for men with confirmed hypogonadism, as discussed in Section III.K.

APC and NCPA appreciate the opportunity to provide these comments and would be pleased to engage further with FDA and other stakeholders on scientific and clinical issues surrounding TRT.

VI. REFERENCES

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