

Testosterone Replacement Therapy: Current Regulatory Landscape

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Objectives

- Summarize current class indication for testosterone replacement therapy (TRT) products
- Outline the current TRT drug development paradigm
- Summarize approved TRT products for pediatric use
- Outline pediatric drug regulations

Hypogonadism – Definition

- Testosterone and its reduced metabolite, dihydrotestosterone (DHT), are required for the development and maintenance of male sexual characteristics.
- Hypogonadism: “A clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone (T) (T deficiency) and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic–pituitary–testicular axis.” [Endocrine Society]¹
- Inadequate/absent production by the testis: primary hypogonadism,
Abnormalities at the hypothalamic or pituitary level: secondary hypogonadism.
- Both types of hypogonadism: congenital (genetic) or acquired

Class Indication

“Drug is an androgen indicated for **replacement therapy** in adult males for conditions associated with a deficiency or absence of endogenous testosterone

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions **such as cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals.** These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing (LHRH) deficiency or **pituitary-hypothalamic injury from tumors, trauma, or radiation.** These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.”

TRT Drug Development Paradigm

- Basic premise: Testosterone (T) products are to be used as **replacement therapy** in men with **specific** hypogonadal conditions associated with deficient or absent testosterone
- FDA requires Sponsors to demonstrate only that a T product reliably and safely increases serum T concentrations into the normal range for healthy, eugonadal men
 - **Primary efficacy measure: Pharmacokinetic (PK) assessment of serum T**
- For the current T replacement indication, FDA does **NOT** require demonstration of benefit **by any clinical efficacy measure**
- Rationale: T replacement therapy (TRT) in men with specific hypogonadal conditions is long-accepted, efficacious therapy

Source: Hirsch MS, Nguyen CP. Advisory Committee. Clinical Background Document. Testosterone Replacement Therapy: Clinical Development and Target Population. Joint Meeting for Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSARM AC). September 17, 2014. Available at: <https://wayback.archive-it.org/7993/20170405210613/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM412536.pdf>

TRT Drug Development Paradigm – 2

Elements of a typical Phase 3 TRT study

- **Design:** open-label, single-arm, several “periods”
- **Duration:** dose titration (6 to 8 weeks) , stable dose (6 to 8 weeks), and safety extension (12 to 36 weeks) periods
- **Number of subjects:** 100 (to several hundred)
- **Eligibility criteria:** adult hypogonadal males, average morning serum T (at least 2 draws) below the normal range – usually < 300 ng/dL

In most subjects: a specific hypogonadism etiology is not known (“idiopathic” hypogonadism)

- **Efficacy endpoints:** Serum testosterone concentrations
(C_{avg} and C_{max})

TRT: Approved Pediatric Use – 1

- Two products:
 - Testosterone enanthate (TE) intramuscular injection
 - Implantable testosterone pellets

- Predicated on the premise that if either primary or secondary hypogonadism “occurs prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics”.^{1,2}

- Both products are also approved “to stimulate puberty in carefully selected males with clear evidence of delayed puberty”.^{1,2}

- FDA-approved labeling recommends that “An X-ray of the hand and wrist to determine bone age should be obtained every six months to assess the effect of treatment on the epiphyseal centers”.^{1,2}



TRT: Approved Pediatric Use – 2

- Testosterone enanthate (TE) was approved in 1953 and the testosterone pellet in 1942, prior to the 1962 Kefauver-Harris Drug Control Act requiring that approved drugs be efficacious as well as safe.
- TE and the testosterone pellet remained approved drugs after undergoing FDA's Drug Efficacy Study Implementation (DESI) evaluation.

TRT: Approved Pediatric Use – 3

- Unclear if there was clinical trial evidence supporting the approval of TE or the testosterone pellet for pediatric patients at the time the original FDA approvals were granted.
- Although approved, the evidence of these drugs' efficacy and safety is unlikely to align with current standards for approval in pediatric patients.
- All other TRT products indicate that “*safety and efficacy in males less than 18 years old have not been established*” and warn that improper use of testosterone in adolescents has been associated with acceleration of bone age and premature closure of epiphyses.

Pediatric Drug Development Regulations*

*Slides courtesy of the Division of
Pediatric and Maternal Health



U.S. Pediatric Drug/Biologic Approval

- Pediatric Age (drugs and biologics)
 - Birth to 16 years* of age, inclusive [21 CFR 201.57(c)(9)(iv)]
- Pediatric product development is held to same evidentiary standard as adult product development
- A product approved for children must:
 - Demonstrate substantial evidence of effectiveness/clinical benefit (21CFR 314.50)



Pediatric Research Equity Act (PREA)

Under PREA, pediatric studies are required* when a product contains any of the following:

- New indication
- New dosage form
- New dosing regimen
- New route of administration
- New active ingredient

*Exceptions for drugs with orphan designation or for when a condition does not exist in children (e.g., prostate cancer)

Best Pharmaceuticals for Children Act (BPCA)

- FDA can issue a Written request (WR) requesting a company voluntarily conduct pediatric studies for all approved and unapproved indications for which active moiety may have health benefit in pediatric patients
 - WR can be issued for on- and off-patent products
 - Patent exclusivity may be attached

Pediatric Drug Legislations

- PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only for indication(s) under review or being developed in adults**
- ****Does not** apply to certain orphan indications
- Pediatric studies must be labeled

- BPCA

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire active moiety and **may include other indications**
- Studies **may be requested** for orphan indications
- Pediatric studies must be labeled



Substantial Evidence of Effectiveness

- Generally, substantial evidence of effectiveness is established through two adequate and well-controlled clinical trials in an affected population.
- For some pediatric conditions, FDA has established an alternative framework for establishing efficacy when disease manifestations and expected response to treatment in affected children and adults expected to be similar: **Extrapolation**

Extrapolation of Effectiveness

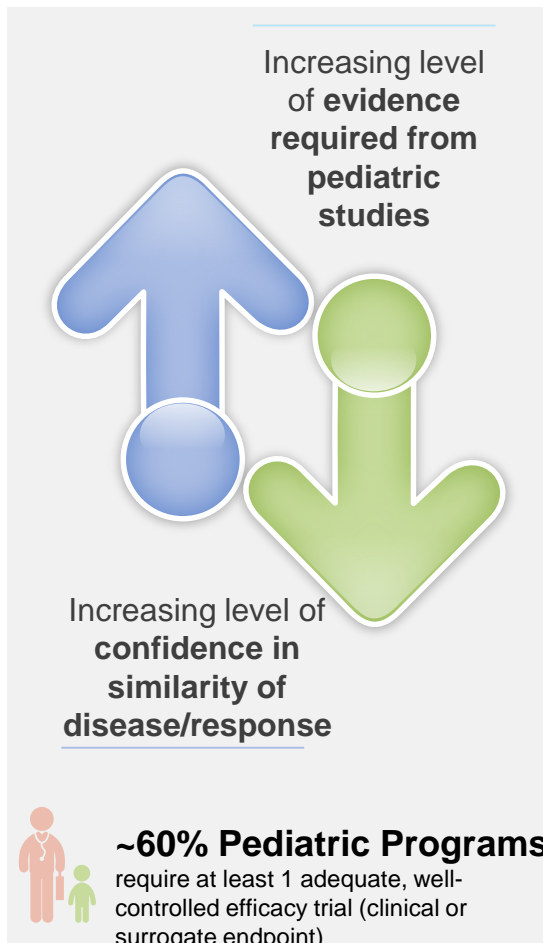
Data supporting disease and response similarity

- Evidence of common pathophysiology, course, and progression of disease/condition
- For example, similar endpoints, mode of drug/biologic action, ontogeny of biomarker expression, experience with drugs in the same therapeutic class

If disease/response are similar, what data are needed to support approval?

- Same pharmacodynamic (PD)/Biomarker endpoint in pediatric and adult patients
- Similar PD effect, similar exposures where relevant

Extrapolation Approaches in Pediatric Programs



1 or more adequate-well controlled studies powered on a clinically meaningful endpoint

Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, polyarticular JIA (pJIA), bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial seizures (<4 y/o), respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.



1 or more adequate-well controlled studies powered on a surrogate endpoint

Diabetes, anemia, idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.



Controlled study without formal statistical power

Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.



Descriptive efficacy study without concurrent control

Plaque psoriasis, Neurogenic detrusor over-activity, pJIA (NSAIDs), etc.



Small dose-ranging studies (randomization to multiple dose levels)

Sedation, ulcerative colitis, Crohn's, etc.



Small PK/PD studies (single dose level matching adult exposures)

HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension,



PK/safety only (single dose level matching adult exposures)

gastroesophageal reflux disease, bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

List partially adapted from Dunne et al. *Pediatrics* 2011

When Efficacy Cannot Be Extrapolated



If efficacy has NOT been demonstrated in adults (or another pediatric population) for the same indication

- Extrapolation of efficacy is not justified
- Adequate and well-controlled trials in pediatric patients are needed

Dosing

- NOT extrapolated from adults
- Obtain pharmacokinetic data to support dose selection in pediatric patients
 - Target exposures at doses found to be effective in adults
- Studies performed in pediatric patients with condition of interest (not healthy children)
- Modeling and simulation may be useful for dose selection and improving study design

Safety

- NOT extrapolated from adults
- Safety data are needed to evaluate the safety of all proposed doses to be used in pediatric patients
 - Data should include the pediatric patient population (indication) expected to use the drug
 - Clinical studies should be large enough and of long enough duration to detect common and potentially infrequent but not necessarily rare adverse events
- Existing data (e.g., published literature, registry) may be used as supportive data



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