MINUTES OF THE PEDIATRIC ADVISORY COMMITTEE (PAC)
The public meeting was convened from 1 pm to 2 pm April 8, 2019

Members Present (voting)	**Temporary Voting Members**
Robert Dracker, MD, MHA, MBA, CPI (*Chair)* Premchand Anne, MD, MBA, MPH, FACC David Callahan, MD Mary Cataletto, MD, FAAP Randall Flick, MD, MPH Peter Havens, MD, MS Sarah Hoehn, MD, MBe, FAAP Randi Oster, MBA Wael Sayej, MD Christy Turer, MD, MHS, FAAP, FTOS Kelly Wade, MD, PhD	David Cooke, MD Angela Delaney, MD Peggy DiCapua Richard Holubkov, PhD James McGough, MD **Non Voting Members** Bridgette Jones, MD, MSc, FAAAAI, FAAP Ronald Portman, M.D., F.A.A.P. **Designated Federal Officer (DFO)** Marieann Brill, MBA, RAC, MT(ASCP)

U.S. Food and Drug Administration (FDA participants)

Office of Pediatric Therapeutics	**CDER OSE**	**CDER DBRUP**
Susan McCune, MD **CDER DPMH** John Alexander, MD., MPH Ethan D. Hausman, MD	Corrine Woods, RPh, MPH	Christine P. Nguyen, MD **CDER DMEP** Ovidiu Galescu, MD, MS John Sharretts, MD

Welcome and Introductory Remarks

- Robert Dracker, Chair, Pediatric Advisory Committee opened the meeting. Dr Dracker directed those participating in the meeting and the audience to press representative Lyndsay Meyer, Press Officer, OC/OEA/OMA (who was not then present).
- Marieann Brill, Designated Federal Officer (DFO), read the usual, customary, and required disclosures and conflict of interest statement.
- Susan McCune, MD, Director gave opening remarks and personnel updates. Acknowledgment plaques and letters of appreciation were given to Dr. Dracker, Dr. Cataletto, and Dr. Jones. Dr. Judith Cope was given a plaque and letter before she left OPT for CBER
    - There were 16 CDER; 3 CBER; 3 CDRH web posted reviews (https://www.fda.gov/advisory-committees/pediatric-advisory-committee/web-posted-pediatric-safety-reviews).
    - There is a FDA workshop on Youth Tobacco Cessation: Science and Treatment strategies scheduled for May 15, 2019 and open for registration (https://www.fda.gov/tobacco-products/youth-and-tobacco/fdas-youth-tobacco-prevention-plan).
    - Non-compliance letters: 31 CDER; 2 CBER

Discussion of Testosterone Replacement Therapy in Adolescent Males

Session 1: FDA Presentations

- Christine P. Nguyen, MD, Deputy Director for Safety, DBRUP, "Testosterone Replacement Therapy: Current Regulatory Landscape":
    - Dr. Nguyen summarized the current class indication for testosterone replacement therapy (TRT) products; outlined the current TRT drug development paradigm for adults; summarized approved TRT products for pediatric use; and summarized pediatric drug regulations.
- Ovidiu Galescu, MD, MS, Medical Officer, DMEP, "Pediatric Male Hypogonadism":
    - Dr. Galescu summarized pediatric male hypogonadism and highlighted conditions for which there is a current unmet medical need.
- Corinne Woods, RPh, MPH, Drug Utilization Analyst, DEPI II, "Testosterone Utilization Patterns Among Pediatric Patients":
    - Ms. Woods summarized data on the reported reasons for use of testosterone products in pediatric males

A brief summary of the Committee's discussion after the morning session is presented below. The final minutes will include the text of the discussion.

Committee members agreed that some form of pediatric extrapolation of efficacy appears to be generally acceptable, and development paradigms could include a pharmacokinetic (PK) and safety study, a PK/pharmacodynamic (PD) matching and safety study, or powered efficacy and safety studies. For any development strategy the Agency recommends, the Committee reached consensus that long-term postmarketing safety studies should be undertaken; one member commented that postmarketing studies could take the form of a registry. One potential safety issue raised by one Committee member was cardiac risk; however, several other Committee members felt that the risk was likely low.

The Committee observed that pubertal progression and testosterone levels in males at any particular Tanner pubertal stage (i.e., stages 2 through 5) are variable which could have implications on study design; however, the Committee commented that the two most directly observable clinical endpoints could be attainment of normal estimated height or successful progression through pubertal stages within a defined time period.

Session 2: Expert Presentations

- Yee-Ming Chan, MD, PHD, Assistant Professor of Pediatrics, Harvard Medical School, "Management of Permanent Hypogonadism in Boys"
    - Dr. Chan reviewed normal male reproductive physiology, from the neonatal period through puberty, the causes and physiology of congenital and acquired testosterone deficiency syndromes in boys, and drugs commonly used to treat these conditions. Dr. Chan also discussed medication management of such patients including labeled and off-label use of drugs.

Open Public Hearing

- **One speaker: see final minutes.**

Industry Presentation

- Alan D. Rogol, MD, PhD, Professor Emeritus (Pediatrics and Pharmacology) University of Virginia, "Testosterone and Male Pubertal Maturation"

- Dr. Rogol reviewed the physiology of testosterone and its relation to male pubertal development. Dr. Rogol noted that most available testosterone products have a limitation of use and are not recommended for patients < 18 years.
- While idiopathic hypogonadotropic hypogonadism (IHH) is labeled, constitutional delay of growth and puberty (CDGP) is not labeled.
- Dr. Rogol stated that CDGP and IHH may only be separable diagnoses upon retrospective analyses once children age out of the pediatric population; particularly when family growth histories and early childhood growth histories are not available.

Session 3: Panel Discussion

Dr. Draker and Dr. Alexander presented the following topics to the Committee for discussion. No voting questions were presented to the Committee.

1. The goal of a pediatric development program with testosterone therapy is to obtain evidence to guide the safe and effective use of such therapy in boys with genetic or structural causes of hypogonadism. Therefore, in consideration of the information provided today, please discuss the following:

- Study design and study population (eligibility criteria)
- The appropriate efficacy endpoints
- The appropriate safety endpoints
- Duration of safety follow up
- Estimated trial sample size

2. Given the information provided today and the study design elements in Question 1 above, please discuss the feasibility issues related to the conduct of such a trial, including:

- Size of a population of boys eligible to be enrolled in the trial
- Recruitment issues

3. Given the known complications of testosterone therapy in pediatric patients (e.g., premature growth plate failure and short stature) what postmarketing safety evaluation(s) do you recommend? Please provide a rationale for your response.

Key elements of the discussion are presented below. For a comprehensive presentation of the discussions, refer to the transcript of the meeting.

The Committee commented that several types of study design might be possible to establish the effectiveness of a new product.

If the Agency were to accept the effectiveness of the two products currently indicated for use in pediatric patients, one approach could be a PK matching and safety study comparing the candidate product to one of the currently indicated and marketed products. This might be adequate to establish dose, effectiveness and safety.

Committee members noted a limitation of this approach is that currently marketed products appear to be used (e.g., monthly injection) in a fashion that does not mirror daily physiologic values. One member asked if that mattered since “we know” the drugs work? Panelist and experts eventually noted that dose titration in pediatrics tends to be

empiric, rather than being based on PD. Discussants also noted that bioavailability of intramuscular formulations is nearly 100%. Therefore, PK studies could help characterize differences in bioavailability of new formulations in children versus adults to help guide a titration scheme for pediatric use.

The Agency could also request a PK/PD study either as a dose ranging study with the candidate drug or in comparison to one of the two labeled drugs. The committee came to no consensus on an appropriate PD marker.

The Agency could also request a study with a clinical endpoint. The committee came to no consensus on an appropriate clinical endpoint.

One Committee member commented that candidate PD endpoints and clinical endpoints appear to be the same (for example: height, initiation of puberty, initiation and completion of puberty). One Committee member stated that if a clinical endpoint were required, the study might need to last 2 to 3 years in order to approximate normal male progression through Tanner stages (that is, from the first recognition of Tanner 2 to Tanner 4 or 5).

In all scenarios the Committee deferred commenting on statistical design and the number of patients that might be needed.

The Committee consensus seemed to accept that a study to evaluate safety and PK in the adolescent population could be sufficient to support the safety and effectiveness of testosterone replacement for adolescents with hypogonadotropic hypogonadism. A long-term safety follow-up study, perhaps in the form of a registry, might be needed to characterize long-term risks.

Dr. Chan noted that his clinical center receives approximately 50 new patients with primary or secondary hypogonadotropic hypogonadism per year.

Adjournment

- Robert Dracker, Chair, Pediatric Advisory Committee

These summary minutes for the April 8, 2019 meeting of the PAC were approved on June 6, 2019.

I certify that I attended the April 8, 2019 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

/s/
Marieann Brill, MBA, RAC, MT(ASCP)
Designated Federal Officer, PAC

/s/
Robert Dracker, MD, MHA, MBA, CPI
Chair, PAC