Early Experience of the RACE for Children Act: Accelerating Initiation of Pediatric Investigations of Novel Cancer Drugs

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DISCLAIMER

- No financial interests to disclose
- Opinions presented represent those of the speaker and do not necessarily represent the position of the FDA

FDA Advisory Committee Consensus Statement

Pediatric *oncology drug development should generally be* ***coordinated*** *with oncology drug development for* ***adults****, as part of an* ***overall drug development plan***

Cancer Drug Development for Children and Adolescents

- Widely leverages adult drug discovery and development-limited opportunities for extrapolation and limited pre-clinical testing in pediatric models
- **Delays in initial pediatric evaluation**
- Many new targeted agents likely applicable to cancers in children but **delayed application of new drug development paradigm to pediatric cancer**
- **Impact of legislative initiatives (PREA and BPCA) which support pediatric drug development has been markedly less obvious in Oncology than in other clinical areas**

Changed Cancer Drug Development Paradigm

- **Genomic/proteomic profiling of human cancers has resulted in identification of highly specific targeted agents**
- Large treatment effects observed in small subsets of patients leading to drug approvals in defined cohorts; seamless, adaptive study designs
- **Approvals based on trial results of biomarker-enriched patient populations**
- **Precision Cancer Medicine**
- Transformative in NSCLC, Melanoma, AML
- **Tissue/histology agnostic** drug development: expanded opportunities for pediatric cancer

RACE for Children Act

- Incorporated as Title V Sec. 504 of the **FDA Reauthorization Act (FDARA),** enacted August 18, 2017
- Amends Pediatric Research Equity Act **PREA**(Sec. 505B of the FD&C Act) **effective August 18, 2020**
- **Requires** evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer" when the subject of an initial NDA/BLA
- **Molecularly targeted pediatric cancer investigation**: clinically meaningful study data, "using appropriate formulations, regarding dosing, safety and **preliminary efficacy** to inform potential pediatric labeling." [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].
- Study to be described in Agreed Initial Pediatric Study Plan (**iPSP**) and data to be included as part of planned application.
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Implementation

- Establish with NCI, update regularly, and post on FDA website a **list of "relevant" targets** (1 year)
- Establish and post a **list of targets (non-relevant) leading to waivers** of pediatric studies (1 year)
- Lists posted on FDA's OCE website Pediatric Oncology Program www.fda.gov/pedonc
- **Develop a computable format in concert with NCI, CCDI's Molecular Targets Platform (based on Open Target) Enable on-going recommendations for addition/deletion . Open FDA docket for comments on existing targets and suggestions for additions/deletions**
- Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, and advocates on implementation
- Issue guidance on implementation **Final guidance published May, 2021**

  https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

Sec. 503 Early Advice Meetings

- Focus on clarifying iPSP requirements for **original** NDA/BLAs to be submitted on/after Aug. 18, 2020 resulting from PREA amendments
- **Scheduled and held within 30 days of request**
- Briefing Document and Questions required
- Meeting request to Review Division; scheduled with and by OCE Pediatric Oncology Program at OCEPerc@fda.hhs.gov
- Internal meeting scheduled with Review Division
- Written responses to questions prior to meeting
- Meeting management and minutes responsibility of OCE Pediatric Oncology Program

Early Advice Meetings

As of August 2021 (First meeting 8/21/2019)

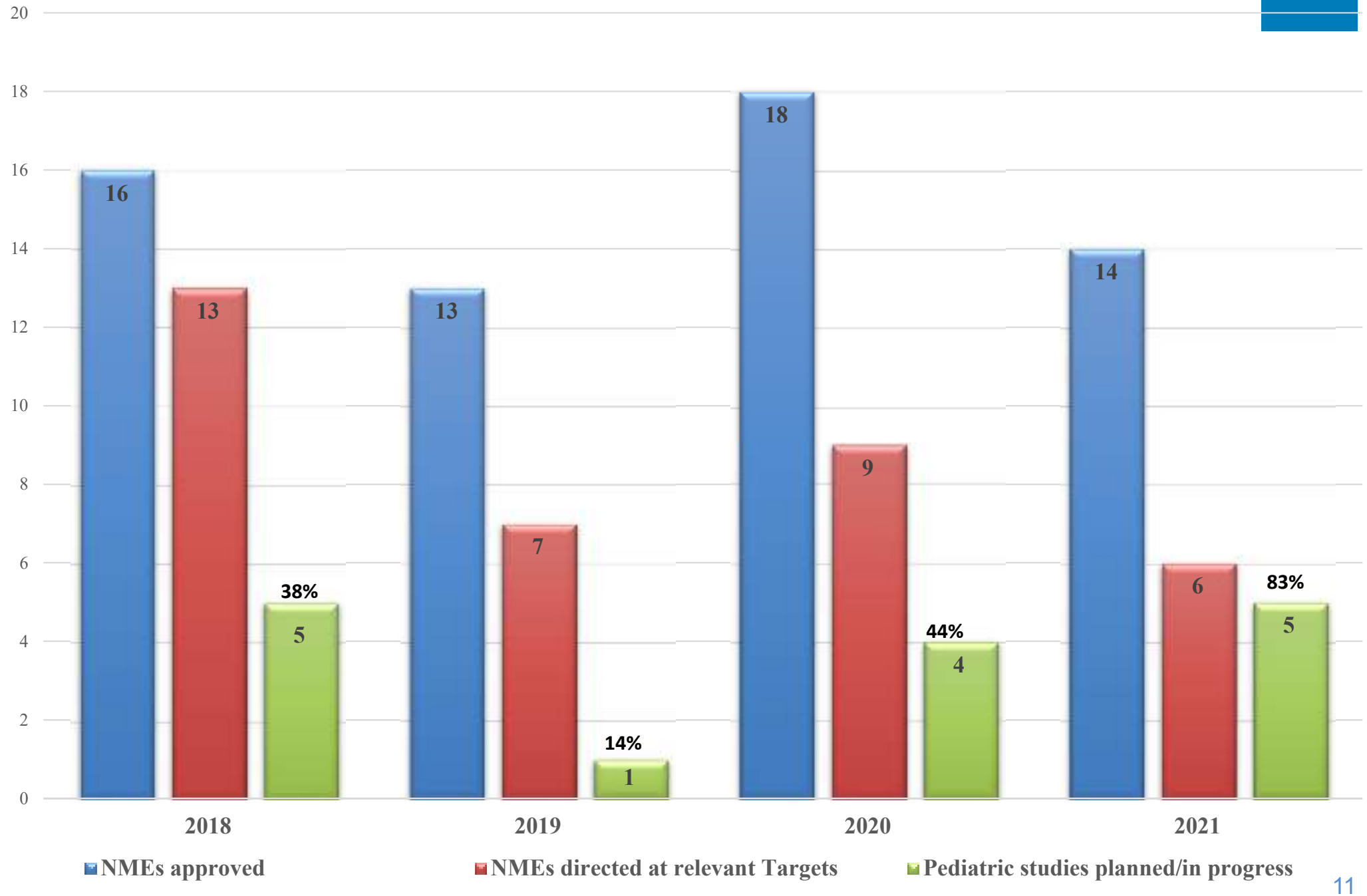
Type of Meeting	No.
Type F Meetings	28
Distinct Molecules (new active ingredients)	28
Products for adult ST indications	18
Products for adult hematological malignancies	10
Planned pediatric studies	13
(iPSPs reviewed)	5
Planned considerations for waiver	15

Agreed iPSPs for NMEs
August 2020 - January 2022

Type of Review	Number
Agreed iPSPs for initial applications of NMEs	26
Products directed at non-relevant targets (Automatic Full Waivers)	8
Products directed at relevant molecular targets	18
Pediatric studies: 1 focused pediatric development; 11 proposed (1 extrapolation, 2 studies in progress)	12
Deferrals	7
Partial Waivers	6
Full Waivers*	6

*Same in Class

Approved Novel Cancer Drugs and Early Pediatric Investigatons



Implementation/Future Considerations

- **Promising trend for commitment to early pediatric studies**
- **Definitive pediatric development through BPCA remains voluntary**
- Impact of RACE requires **FDA regulatory flexibility** and innovation in study design: *platform trials, synthetic controls, Bayesian adaptive designs, Relaxing type 1 error for RCTs.*
- **Global collaboration: International clinical trials and regulatory alignment**
- While single agent studies are critical, clinical advances require investigations of combinatorial approaches **supported by sound biologic rationale and pre-clinical testing data.**

Global Pediatric Neuro-Oncology Network (AAADV, Sept. 2021)

- Multi-stakeholder session
- Addresses unmet clinical need: brain tumors now cause most childhood cancer deaths
- Established networks in U.S. and EU(COG,PBTC, SIOPE, PNOC, ReMission, CONNECT)
- Developing regional networks in India (Tata Mem'l, Mumbai Apollo Hospital, Chennai)
- Industry interest and commitment

Global Pediatric Neuro-Oncology Network: Challenges

- Defining scope/breadth of outreach
- Clarification of objectives/mission
- Diverse access to core diagnostic and therapeutic capabilities (XRT, Surgery, Path)
- Access to essential and investigational medicines
- Multiple brain tumor histologies; now with new genomic classification
- Biopsies and CDx testing for biomarker-directed studies
- Centralized data capture and management/Data sharing
- Central Pathology and Imaging review
- Cultural and social barriers to care: impact on research

Complementary Efforts to Advance Global Collaboration

- ACCELERATE Platform: International Collaboration Working Group
- SIOP **PARC** Program (**P**rogram for **A**dvancing **R**esearch **C**apacity) for LIC/MICs
- Initiative linked to SIOP's role in the WHO Global Initiative on Childhood Cancer (GICC) and improving research to advance cure rates
- Goals: 1) Building capacity, 2) Creating research infrastructure, 3) Addressing access issues, 4)Expending enrollment on clinical trials required for approval/marketing authorization of new cancer drugs for children
- Neuro-Oncology