FDARA 2017 and the RACE for Children Act: Implications for Pediatric Cancer Drug Development

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Disclaimer

• I have no financial interests to disclose
• I will not be presenting the off label use of any approved drugs
Outline

• Brief summary of U.S. legislation related to drug development for children
• Move from indication to MOA-based trigger for PREA requirements for pediatric studies: Voluntary to Mandatory
• Legislative mandates of FDARA to implement new pediatric provisions Title V
• Update on current plans
• Potential global implications: strategies for coordination
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**
# U.S. Legislation and Pediatric Drug Development

<table>
<thead>
<tr>
<th>PREA</th>
<th>BPCA</th>
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<tbody>
<tr>
<td>- Drugs and biologics</td>
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<td>- <strong>Mandatory</strong> studies</td>
<td>- <strong>Voluntary</strong> studies</td>
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<tr>
<td>- Requires studies <strong>only on indication(s) under review</strong></td>
<td>- Studies relate to entire moiety and <strong>may expand indications</strong></td>
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<td>- <strong>Orphan indications exempt</strong> from studies</td>
<td>- Studies may be requested for orphan indications</td>
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<td>- Pediatric studies must be labeled</td>
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Current FDA Initiatives

• Increased role in promoting **collaborative** approach to **timely** pediatric drug development

• Optimizing regulatory authority of **BPCA**: Written Requests only since **PREA** of no relevance to oncology

• **Proactive** identification of promising new treatments and engagement with industry/academia/advocacy groups to study these products earlier: BPCA Pediatric Oncology Working Group and Pediatric Subcommittee of ODAC

• Providing technical advice on key legislative initiatives

• Harnessing regulatory science to meet drug development challenges
Delayed Pediatric Cancer Drug Development Due to Orphan Exemption

- brentuximab vedotin (ADCETRIS)
- blinatumomab (BLINCYTO)
- inotuzumab ozogamycin (BESPONSA)
- liposomal cytarabine/DNR (VYXEOS)
- enasidenib (IDHIFA)
- midostaurin (RYDAPT)
- olaratumab (LARTRUVO)
- ipilimumab (YERVOY)
- pembrolizumab (KAYTRUDA)
RACE for Children Act:

- Incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted August 18, 2017
- **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.”
- **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)].
- Elimination of **orphan exemption from pediatric studies** for cancer drugs directed at relevant molecular targets.
Implications

• Establish with NCI, update regularly, and post on FDA website a list of “relevant” targets (1 year)
• Establish and post a list of non-relevant targets leading to waivers for pediatric studies (1 year)
• Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates
• Convene an open public meeting to refine/generate lists (1 year)
• Issue guidance on implementation (2 years)
Status

• Introductory workshop planning in progress (February 20, 2018): Developing a framework for target selection/designation
• Target classification and criteria for determining relevance, process for updating lists, and additional considerations for decision-making for pediatric evaluation: Friends of Cancer Research
• Open Public meeting: 1) April 19, 2018 at FDA - Review molecular target lists. 2) Pediatric subcommittee of ODAC, June 18/19, 2018 - review/comment on lists and considerations; process for prioritizing same in class agents - working with external constituents
• Planning and implementation coordinated with internal FDA programs - OPT, DPMH, ORP, and OCC
• Advising sponsors of new conditions and requirements for iPSPs for new applications with planned submission dates after 8/18/2018
Molecular Target

A molecule in human cells that is intrinsically associated with a particular disease process such as etiology, progression, and/or drug resistance. To be referred to as a target, there must be evidence that by addressing the target with a small molecule, biologic product, or other treatment intervention, a desired therapeutic effect is produced resulting in the alteration of the disease process.
Strategies for Identification

• Gene sequencing
• Expression profiling
• CMA
• Focused proteomics
• Pathway/phenotypic analysis
• Functional screening (siRNA, shRNA, CRISPR)
• *In vitro or in vivo validation*
Target Classification

• Resulting from specific gene abnormalities; present in a critical biologically related pathway or exhibit a synthetic, lethal relationship to a gene abnormality

• Intrinsic to cancer cell lineage or developmental stage

• Contributing to functional aspects of tumor microenvironment (stroma, infiltrating immune cells)

• Essential elements of cancer (and normal) cells
Factors Related to Relevance

- Identification of the target in a pediatric cancer (gene defect, intrinsic or differential expression by cancer cell)
- Target function relevant to etiology or progression
- Effect of target modulation; in vivo, in vitro, synergy in biologic/rational combination
- Clinical experience; adult and pediatric
- Existence of predictive biomarkers
- Cell surface access of immune-directed targets
• About 182 possible targets identified thus far.
Considerations for Application of Target List to Product Development for Children

- Biologic plausibility
- Evidence of serious, deleterious (lethal) effects on critical developmental processes
- Risk: benefit analysis
- Toxicity profile
- Formulation issues
- Pre-clinical studies and access to product
- International coordination: global development
Successful Implementation

• Transparent process
• Respect/anticipate emerging scientific discovery
• International collaboration in designation and prioritization
• Recognize/address anticipated, potentially adverse consequences
• Global coordination/collaboration