Implementation of FDARA Title V: Evolving U.S. Regulatory Framework for Pediatric Assessment of New Oncology Products

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Cancer Drug Development for Children and Adolescents

- Well recognized, long-standing challenges- biologic, societal, economic
- **Widely leverages adult drug discovery/development- limited opportunities for extrapolation and limited pre-clinical testing in pediatric models**
- **Impact of legislative initiatives which support pediatric drug development has been markedly less obvious in Oncology than in other clinical areas.**
- Many targeted agents likely applicable to cancers in children

U.S. Legislation and Pediatric Drug Development

PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication(s) under review**
- **Orphan indications exempt** from studies
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary** studies with incentive
- Studies relate to entire moiety and **may expand indications**
- Studies may be **requested** for orphan indications
- Pediatric studies must be labeled

RACE for Children Act:

- Incorporated as Title V Sec. 504 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 for pediatric studies** for cancer drugs directed at relevant molecular targets.

Molecular Target Definition

- 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

Statutory Requirements for FDA

- 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)
- Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates on implementation and required studies
- Convene an open public meeting to generate/finalize lists (1 year)
- Issue guidance on implementation (2 years)

Current FDA Efforts: Implementation

- Open Public meetings:
  1)April 20, 2018 at FDA - Review candidate molecular target lists.
  2) **Pediatric Subcommittee of ODAC, June 20, 2018** - finalize lists; considerations for **application of target lists**; process for **prioritization** including same in class agents- working with external constituents (multi-stakeholder); a process to support **international collaboration/coordination-** Global Drug Development and non-alignment of regulatory requirements/timelines
- Planning and implementation coordinated with internal FDA programs- OHOP/OCE, OPT, OCP, DPMH, ORP, and OCC
- **Focus on accelerating appropriate initial pediatric evaluations early in development timeline not increasing number of pediatric phase 1 studies**
- Advising sponsors of new conditions and requirements for iPSPs for **new** applications with planned submission dates after 8/18/2020

Friends of Cancer Research Workshop

- Forum for scientific **discussion and multi-stakeholder exchange**
- Consider a **framework** for defining pediatric **"relevance"** for current and future molecular targets and **classification**: tool to organize totality of evidence: **Target association, function/mechanism, non-clinical data, adult clinical experience, predictive biomarkers, agent availability**
- Address additional factors which may impact decision-making and some anticipated consequences
- Discussions not focused on specific diseases or strategies for therapeutic investigation in a single disease area

Target Lists

- Statutory requirement to purportedly address regulatory uncertainty for Industry and **guide (not dictate)** early decision-making
- **Designation as relevant neither an absolute nor exclusive requirement for decisions related to pediatric evaluation:** studies of new products may be required if directed at a target **not** on the list and waivers likely for products directed at targets considered relevant
- **Not envisioned to restrict authority or flexibility**
- Relevant molecular targets- independent of agent and/or biomarker availability
- **Candidate** Target List constructed by OCE with NCI and input from international content experts (Investigators)
- Published, peer-reviewed literature, abstracts, public databases
- No pre-specified **minimum evidence base**
- Further recommendations received via NCI RFI through May 30, 2018

Gene Abnormality

Target Symbol	Gene Abnormality
ABL1/2	ABL1/2 gene fusions (BCR-ABL1, etc.)
ACVR1	ACVR1
ALK	ALK and ALK gene fusions
ASCL1	ASCL1 gene
BRAF	BRAF
BRD3-NUTM1	BRD3-NUTM1
BRD4-NUTM1	BRD4-NUTM1
CCND1,2	CCND1,2
CDK12	EWSR1-FLI1
c-KIT or KIT	c-KIT or KIT
CSF1R	CSF1R gene fusions
CTNNB1 (β-catenin)	CTNNB1

Target Symbol	Gene Abnormality
DDX3X	DDX3X
DOT1L	MLL gene fusions
EGFR	EGFR
ERK	BRAF, MAP2K1
ETS gene fusions	ETS fusions (ERG, FLI1, ETV1)
EWSR1-FLI1	EWSR1-FLI1
EZH2	SMARCB1, SMARCA4
FGFR	FGFR and FGFR gene fusions
FLT3	FLK2, STK1, CD135
Gamma secretase	NOTCH1 and FBXW7
GFI1	GFI1
GFI1B	GFI1B

Gene Abnormality

Target Symbol	Gene Abnormality
Histone 3 G34R/V	Histone 3 G34R/V
Histone 3 K27M	Histone 3 K27M
IDH1 and IHD2	IDH1 and IDH2
JAK1, 2, and 3	JAK1, 2, and 3
LIN28B	LIN28B
MDM2	MDM2, TP53
MEK	BRAF and BRAF gene fusions, MAP2K1, NF1
Menin	MLL gene fusions
MET	MET
MLL	MLL gene fusions (MLL-AF4/AF9/AF10/ENL/ELL/AF1p/AFX/FKHRL1/SEPT6/GAS7/EEN/CBP/PTD)
mTOR	TSC1, TSC2
MYC	MYC translocations and amplification

Target Symbol	Gene Abnormality
MYCN	MYCN amplification
Neoantigens	MSH2, MLH1, MSH6, PMS2 POLE, and POLD1
NFkappaB	RELA fusion
NOTCH1	NOTCH1, FBXW7
NSD3-NUTM1	NSD3-NUTM1
NT5C2	NT5C2
NTRK	NTRK gene fusions
ODC1	MYC target gene
PARP	BRCA1/2, PALB2, ATM, BRIP1, CHEK2, RAD51, etc.
PAX-FOXO1	PAX-FOXO1
PDGFRA/B	PDGFRA/B gene fusions
PI3Kα	PIK3CA

Gene Abnormality

Target Symbol	Gene Abnormality
PPM1D (WIP1)	PPM1D (WIP1)
RAS	RAS
RET	RET
SH2B3	SH2B3
SHP2	SHP2
Smoothened	PATCH1, SMO
STAT2,3	STAT2,3

Target Symbol	Gene Abnormality
SYT-SSX	SYT-SSX
TERT	TERT
TORC1/2 as distinct from mTOR	TORC1/2
TrkB	TrkB
TP53	TP53
TYK2	TYK2
ZNF532-NUTM1	ZNF532-NUTM1

Cell Lineage

Target Symbol (1)	Target Symbol (2)	Target Symbol (3)	Target Symbol (4)
AKR1C3	CD70	GPNMB	PTEN
BCOR	CD79b	ERBB2 (HER2/Neu)	SYK
BTK	CD123/IL3RA	IL6	WT1
CD7	CD276 (B7-H3)	IL13RA2	YAP1
CD19	Cereblon CBL (E3 Ubiquitine protein ligase)	LRRC15	
CD20	DLL3	MAGE-A3	
CD22	DLK1	MSLN (mesothelin)	
CD30	EGFRvIII	NR5A1 (Steroidogenic factor-1)	
CD33	EPHA2	NY-ESO-1	
CD37	GD2	Olig2	
CD38	GPC2	PIK3CD (PI3 kinase delta)	
CD56	GPC3	PRAME	

Tumor Microenvironment & Immunotherapy

Target Symbol (1)	Target Symbol (2)
B7H3	OX40
CD40	PD-1/PD-L1
CD47	RELA
CD52	RIG-I
CXCR4	STEAP1
CXCL10	STING
CTLA4	TIM3/TIM4
GM-CSF	VEGF
IDO1	VEGFR
IFN-gamma	
IL-2	
LAG3	

Others

Target Symbol (1)	Target Symbol (2)	Target Symbol (3)	Target Symbol (4)
AKT	BMPR	DNA-PK	LSD1
ATM	Brd1	DNMT (DNA methyl transferase)	MCL1
ATR	Brd4	FAK	MCT1 (monocarboxylate transporter 1)
ATRX	CDK4/6	FOLR1 (folate receptor 1)	MEK
AURKA (Aurora kinase A)	CHK1	GSK-3	MIZ1
AURKB (Aurora kinase B)	CDK2	HDAC	MGMT
AXL	CDK7	HIF1A	MLL5
A1/BFL	CDK9	Hippo pathway (YAP, TAZ, TEADs)	MYST3 (MYST histone acetyltransferase (monocytic leukemia)
BAK	CK1	Hsp90	NAMPT
BAX	CK2 (casein kinase 2)	IAPs (inhibitor-of-apoptosis)	NEDD8 activating enzyme (NAE)
BCL2 family members (Bcl-2, Bcl-XL, Mcl-1, A1/BFL, BAK, BAX)	CREBBP/EP300	IGFR-1	PARP
BET bromodomain family	DNA (alkylators)	KDM4A	PDK-1 (3-phosphoinositide-dependent protein kinase 1)

Others

Target Symbol (5)
PI3Kdelta
PIM1
PKA
PKC
PLK1
POL1
PRDM1
PRDM8
PRDM10
PRMT2
PRMT5
Proteasome

Target Symbol (6)
PTPN (protein tyrosine phosphatase)
RPA3
SHP2
SMYD3
Somatostatin Receptor
Survivin (BIRC5)
SUZ12
SWI/SNF
TET2
TGF-beta
Thymidylate synthase
Topoisomerase I/II

Target Symbol (7)
TRAIL
Tubulin
XPO1 (Exportin)
WDR5
WEE1

Automatic Waivers

Target Symbol
AR
ESR1
ESR2
GnRHR
PSA/PSCA/PSMA

Level of Evidence	Description
Level 1	1) Accepted evidence (peer-reviewed publications, abstract of scientific meetings, publicly accessible databases) that the molecular target of interest is expressed in 1 or more childhood cancers. 2) Accepted evidence that inhibition of the target may have a substantial growth effect in human cancer (in vitro and/or in vivo). Preclinical activity documented with use of single agent inhibitors or (for agents lacking single agent activity) in combination demonstrating a supra-additive effect. 3) Clinical evidence of substantial growth effect from target inhibition in 1 or more human cancers. 4) Pre-clinical evidence of anti-tumor activity in pediatric tumor models. 5) Predictive biomarker available for patient selection.
Level 2	1) Criteria 1, 2, 3, as above. Criteria 4 and/or 5 – data may or may not be available.
Level 3	1) Criteria 1 and 2, as above. Data to address criteria 3, 4, & 5 may not be available.
Level 4	1) Criteria 1 and 2, as above. Pre-clinical evidence of activity not demonstrated in any pediatric model systems. No evidence of clinical activity in any tumor systems evaluated.
Level 5	1) Criteria 1 and 2, as above. Data to address criteria 3, 4, & 5, may support target relevance. Prior Clinical trial(s) of drug(s) directed against the target failed to document antitumor activity in one or more pediatric cancers.

Waiver Considerations

- Serious developmental toxicity- consideration for full or age dependent partial waiver
- Second or third “in class” product (single agent) without compelling evidence of substantial differences in efficacy, safety, PK profiles, or formulation to warrant additional pediatric studies
- Feasibility and practicability due to small study populations potentially addressed by limited study requirements and innovative study design and conduct: embedded pediatric trials, expansion cohorts, histology-agnostic development

Publishing and Updating Lists

- Semi-annual public workshops
- Enabling on-going recommendations for addition/deletion
- Lists posted on FDA's OCE website Pediatric Oncology Program
- Opening FDA docket for comments on existing targets and suggestions for additions/deletions

Considerations for Decision-Making and Prioritization

- Likely variable by target class and disease
- Prevalence of target expression in a single disease or across histologies and evidence that target inhibition modulates tumor growth
- Extent of unmet clinical need or potential public health impact
- Availability of and access to agent
- Availability of predictive or response biomarkers
- Collaboration between Industry and clinical investigator community: **Multi-stakeholder input required** to inform FDA decision-making

Considerations for Decision- Making and Prioritization

- Clinical and/or pre-clinical evidence of activity
- Toxicity profile
- Potential benefit:risk assessment
- Formulation
- Multiple agents in class: transparent evaluation of selection criteria in pre-competitive space
- Rare pediatric cancers not well supported by current study platforms; innovative designs/solutions

Addressing Challenges

- Uniform international **master protocols** for biomarker-directed studies- efficient and high quality data
- Increasing **extramural** input while respecting proprietary considerations
- **Early** pipeline presentations; possible Industry collaboration
- Industry-initiated Public Private Partnership

Successful Implementation

- Transparency among all stakeholders
- Address anticipated, potentially adverse consequences
- **Initiate early pediatric pre-clinical testing initiatives - effective Industry-Academic collaboration when necessary (Public-Private Partnerships)**
- Recognize emerging scientific discovery
- **Global development requires international collaboration in designation of relevance, prioritization, and decision-making re. study feasibility and conduct**
- Robust, publicly shared, datasets-genomic, proteomic, pre-clinical testing- all require support and expansion

Global Coordination

- Priority setting of relevant targets through periodic international, multi-stakeholder workshops
- Continue Pediatric Cluster Call discussions of PIPs/iPSPs and provide Common Commentary when requested and appropriate
- Plans for international expansion of the EU ACCELERATE Platform
- Support/encourage international trials when possible; avoid duplication and competition