FDA Briefing Document
Relevant Molecular Targets in Pediatric Cancers: Applicability to Pediatric Therapeutic Investigations Required Under FDARA 2017

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Chair: Dr. Gregory Reaman, MD

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White Oak Campus Building 31
White Oak Great Room A
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

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Pediatric cancer drug development typically leverages adult cancer drug discovery but has lagged far behind development of cancer drugs for adults. To date, the Pediatric Research Equity Act (PREA) has not been an effective mechanism to support the development of drugs for pediatric cancers because the requirement for conduct of pediatric studies is linked to the indication sought in adults and most adult cancers occur rarely, if ever, in children (e.g., cancers of the lung, prostate and breast). Therefore, sponsors obtain waivers for conducting assessments of these drugs in pediatric patients because studies would be infeasible or highly impracticable. Additionally, drugs developed for those rare cancer indications which may occur in both adult and pediatric populations which are frequently granted orphan designation are exempt from the requirements of PREA.

While there has been limited obligation to study investigational cancer therapies in children, incentives exist to promote the development of oncology products for pediatric cancer when these agents are in development or already approved for adult use. The Best Pharmaceuticals for Children Act (BPCA) is a voluntary mechanism which provides incentives in the form of 6 months of exclusivity for marketing to sponsors upon the completion and submission of pediatric studies that meet the terms of a written request from FDA (FD&C Act Sec. 505A, 21USC 355a, FDA Amendments Act (FDAAA) Public Law 110-85). BPCA has been the sole legislative mechanism available to evaluate those oncology products of interest for their potential role in the treatment of malignancies in children and adolescents.

The 2017 enactment of Title V of the Food and Drug Administration Reauthorization Act (FDARA) (FD&C Act Sec. 505B (a)(3), 21 USC 355c (a)(3), Public Law 115-52), which amends the requirement for pediatric assessment of new drugs under the Pediatric Research Equity Act (PREA) based on molecular mechanism of action rather than clinical indication, may dramatically change the landscape for pediatric cancer drug development FDARA has now created a mechanism to expedite the evaluation of novel medicines with the potential to address the unmet need in the pediatric population.

Molecularly targeted agents have advanced the concept of Precision Medicine in oncology. As malignancies occurring in children and adolescents can harbor molecular abnormalities similar to those found in adult cancers, these agents may be relevant to the treatment of pediatric patients with cancer. Although large scale sequencing efforts, such as TARGET, the Pediatric Cancer Genome Project, and the International Cancer Genome Consortium's Pedbrain Tumor and MMML-seq projects provide evidence that the genetic and epigenetic repertoires of driver gene aberrations often differ between adult and pediatric cancers, a growing body of evidence suggests that genetic and other molecular biological vulnerabilities of certain adult cancers may also occur in pediatric cancers, thereby providing opportunities for the use of targeted therapies in select pediatric tumors; up to 50% of pediatric cancers harbor a potentially druggable event. Timely investigation of the antitumor activity of potentially useful targeted drugs and biologics under

development in adults, and of their toxicities relative to the unique growth and developmental considerations of pediatric patients, is warranted for pediatric populations with cancer.

Title V of FDARA has amended PREA to support early evaluation of such drugs by requiring pediatric investigation of appropriate new drugs intended for adults with cancer. The investigations that FDA may require by statute are referred to as **molecularly targeted pediatric** cancer investigations. These investigations may include clinical studies designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling [FDARA Title V Sec 504 (a)(3)(A), FD&C Act Sec. 505B (a)(3)(A), 21 USC 355c(a)(3)(A)]. Importantly, Title V of FDARA also specifies that the requirement for early pediatric investigations of drugs directed at molecular targets considered substantially relevant to the growth or progression of a pediatric cancer be applied, even when the adult indication has received an orphan designation, or when the adult cancer indication does not occur or is biologically different in the pediatric population.

The statute also directs the FDA, in collaboration with the National Cancer Institute (NCI), to establish, publish, and regularly update a list of molecular targets considered, on the basis of data the Agency determines to be adequate, to be substantially relevant to the growth or progression of pediatric cancers, and that may trigger the requirement for pediatric investigations [21 USC 355c (m)(1)(A)]. Molecular targets that are considered "not relevant" to the growth or progression of pediatric cancers will be placed on a second list [21 USC 355c (m)(1)(B)]. The statute does not stipulate that a molecular target to which a specific drug is directed must appear on the relevant target list to require a clinical evaluation of the drug in the pediatric population. Furthermore, presence of a target on the relevant target list does not in itself constitute a requirement for a clinical study.

The FDA is mandated to convene a public meeting no later than 1 year after the date of the enactment of FDARA to solicit views of physicians, academic researchers (including pediatric oncologists and rare disease specialists), patient advocates, industry and other stakeholders for the establishment of the molecular targets lists [21 USC 355c (m)(2)(1)]. This meeting on Molecular Targets in Childhood Cancers is one such meeting and a future public meeting is planned for June 20, 2018 at the meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC).

A Friends of Cancer Research (FOCR)-sponsored multi-stakeholder public workshop held on February 20, 2018, discussed approaches for developing, updating and applying the molecular target list. This meeting included discussions of a framework to assess factors to define molecular targets as substantially relevant or not relevant to the growth or progression of one or more pediatric cancers; proposed processes and timelines for regularly updating the lists of molecular targets; and additional considerations for the application of the molecular target lists to decision-making regarding pediatric evaluation of specific drugs.

Although there may be differences in the way "molecular target" is defined, for the purposes of establishing a list of molecular targets considered to be substantially relevant to the growth or progression of pediatric cancer, a molecular target is defined **as a molecule in human cells that is intrinsically associated with a particular disease process, such as etiology, progression, or drug resistance. To be referred to as a target, there must be evidence that by engaging the target, either with a targeted small molecule, biologic product, or other treatment intervention, a desired therapeutic effect is produced that results in the alteration of the disease process. In other words, a molecule would not be referred to as a molecular target if there is no evidence to inform the hypothesis that its modulation (i.e., inhibition or activation) alters the disease**.

The proposed framework for assessing those factors that may guide the definition of molecular targets as substantially relevant or not relevant to the growth or progression of one or more pediatric cancers includes a classification system to facilitate an organized approach to determination of relevance. Targets may represent the result of specific gene abnormalities, are present in a critical biologically-related pathway of a gene abnormality or exhibit a synthetic lethal relationship to a gene abnormality (**gene abnormality-based targets***)*. Targets can be intrinsic to the cancer cell lineage or developmental stage (**cancer cell lineage-based targets**), or they may be identified in non-cancer cells, such as normal immune cells or supporting cells contributing to the tumor micro-environment (**non-cancer cell targets**). Targets may exist as essential elements of cancer cells as well as some non-cancer cells and are not caused by a specific genetic aberration, such as tubulin or heat-shock proteins (**other targets**).

Evidence of effectiveness for a drug or biologic directed at a molecular target in an adult cancer and identification of the target as substantially relevant for the growth or progression of a pediatric cancer provide a rationale for the agent's evaluation in the pediatric cancer population, regardless of similarity to the histologically-defined cancer found in the adult. Although not a requirement, it is beneficial for sponsors of such an agent to develop *in vitro* and/or *in vivo* data using pediatric non-clinical models to provide increased confidence in either establishing or refuting potential relevance.

Two specific elements of a framework were identified, one that outlines factors that may be useful when determining whether a target is substantially relevant in pediatric cancer and may trigger the requirement for pediatric investigations. The second outlines factors to consider when assessing the available data that may help determine there is insufficient evidence of relevance, and that the target is hence "not relevant". (See Tables 1 and 2)

The FDA, in collaboration with the NCI, is tasked with determining whether a molecular target is or is not considered substantially relevant to the growth or progression of pediatric cancer. FDA has the regulatory authority to determine whether adequate evidence is available to define a target as substantially relevant to require pediatric investigation of a drug directed at that target. Defining a specific evidence standard for determination of target relevance is not feasible for several reasons, including the different classes of targets, variability in evidence base that may exist among targets and between specific target classes, and the fact that emerging science evolves making pre-defined qualifications based on peer-reviewed publications or publicly

available registry data difficult. Several factors may support a scientifically-based and data-driven decision-making approach. These factors are not meant to be either all-inclusive or prescriptive, as there may be additional factors for some specific targets and some factors may not be required for all targets within a class. Table 1 characterizes the factors used in the determination of whether a molecular target is substantially relevant to the growth or progression of pediatric cancers. The framework is not meant to be interpreted as a checklist, and it is important to note that the totality of evidence available may be considered when guiding discussions to determine target relevance. Additionally, the presence of a single factor or a combination of factors may not be sufficient to define relevance.

Table 1: Framework of factors and characteristics that may guide the determination of whether molecular targets are *substantially relevant* in the growth or progression of pediatric cancer

Factors		Considerations
Presence of target		The target has been identified in at least one case of a pediatric cancer
	Target class: Gene abnormality	The gene abnormality has been identified in at least one case of a pediatric cancer
	Target class: Cancer cell lineage	The target is intrinsically and differentially expressed in the cancer of interest compared to normal site-specific tissues.
Function/Mechanism		The biological function of the target is relevant to the etiology and growth of the childhood cancer
	Target class: Gene abnormality	Modulation of the affected gene product or of a critical downstream pathway or correction/deletion of the affected gene defect adversely affects cancer cells
		The presence of the gene abnormality creates a synthetic lethal relationship with another cellular pathway
	Target class: Cancer cell lineage	The target is associated to cancer cell development, growth and survival
Non-clinical evidence		Non-clinical evidence supports relevance of target in one or more pediatric cancers
	In vitro activity	Target modulation shows *in vitro* selectivity for cancer cell lines containing/expressing the molecular target (pediatric or adult cell lines if target is known to be shared by multiple cancer types regardless of patient population) compared to the sensitivity of cell lines not containing/expressing the target
	In vivo activity[1]	Target modulation shows *in vivo* activity manifested as tumor stabilization or regression in models of pediatric cancers with the molecular target of interest (or adult cancer models containing/expressing the target)
	Lack of *in vitro* or *in vivo* activity	For targets for which target modulation does not show *in vivo* or *in vitro* activity, support for relevance may be found in evidence for supra-additive or synergistic activity when target modulation is used in biologically rational combinations
Adult clinical experience		Target modulation by investigational agents known to affect the target, shows clinical activity in specific cancers in adults
Predictive biomarkers		Biomarkers that predict responses to target modulation may be useful in the selection of appropriate pediatric study populations
Location		For immunotherapy targets, the target is expressed on the cell surface (excepting immunotherapies that target intracellular antigens that are displayed as peptides by MHC proteins on the cell surface)
Agent under development		There is an agent in development or proceeding to development that addresses the specific target

[1]The *in vivo* activity should be observed at drug exposures that are relevant to the clinical setting if there is clinical experience with the agent. Prolonged stable disease may be relevant, particularly for agents that induce their anticancer effect through mechanisms other than cancer cell apoptosis.

Because of the potential importance of non-clinical evaluation in contributing to the evidence base for relevance of a molecular target, every effort should be made to ensure sponsors expedite early non-clinical investigation, which could be in collaboration with academic research teams with pediatric expertise in non-clinical testing. The creation of these collaborations and/or partnerships, ideally international in scope, should be explored further as they will be crucial for early testing of non-clinical models, such as patient-derived xenograft models.

Biomarkers that are identified as predictive for the activity of adult cancer targeted agents should also be evaluated for prevalence of expression and potential utility across pediatric cancers. Sponsors are strongly encouraged to test samples from pediatric cancers to determine prevalence, especially when an assay to identify a biomarker is developed in conjunction with the investigational agent and may not be available for use on patient samples by investigators.

There may be evidence available that demonstrates a molecular target is not relevant in pediatric cancers that would prevent it from being added to the substantially relevant molecular target list. The factors listed in Table 2 highlight considerations that may guide the determination of whether a molecular target is not relevant to the growth or progression of pediatric cancer. Again, it is solely the FDA's responsibility to determine what evidence is necessary to determine whether a molecular target is considered not relevant in pediatric cancer, and thus this document does not attempt to define what "adequate evidence" refers to in this context.

Table 2: Framework of factors and characteristics to consider that may guide the determination of whether molecular targets are *not relevant* to the growth or progression of pediatric cancer[1]

Factors	Considerations
Biologically implausible	Molecular targets for which available evidence supports no role for the targets in pediatric cancers (e.g. endocrine/autocrine sex steroid hormonal pathways that are known to be drivers of specific adult cancer types but are very rarely to never observed in pediatric cancers)
Non-clinical evidence	Evidence of lack of activity of an agent in development against a specific target in non-clinical systems could be a component of the evidence base used to determine that a specific molecular target may not be relevant to the growth or progression of a pediatric cancer.
Adult clinical evidence	Evidence of lack of clinical activity of an agent in development against a specific target could be a component of the evidence base used to determine that a specific molecular target may not be relevant to the growth or progression of a pediatric cancer.

[1]There may be agents that are relevant to the growth or progression of disease but that would not be considered for development because of their association with developmental processes such that their inhibition would raise concerns about irreversibly deleterious developmental effects and subsequent growth-related toxicities.

Molecular targets which lack sufficient evidence to make a determination of "substantially relevant" or "not relevant" will not be included in either list. Decisions regarding relevance of these targets to the growth or progression of pediatric cancers will be made when there is an adequate evidence base to make such a determination. Sponsors and investigators are strongly encouraged to investigate the potential relevance of new and currently unlisted targets as expeditiously as possible, especially when there are early non-clinical or clinical signals of activity.

To ensure molecular targets lists are updated in a timely fashion using the most relevant evidence available in light of the rapid pace of scientific advances, three distinct suggestions emerged:

- The first suggestion includes a semi-annual or annual public workshop at which all stakeholders could discuss potential changes to the molecular targets lists. The FDA is responsible for convening and presiding over this semi-annual or annual meeting, which may occur following a national or international scientific meeting. This meeting will seek input from individual stakeholders on advances in relevant scientific evidence that may impact the inclusion of one or more molecular targets on the current published lists, including potential relevance of unlisted targets. Decisions related to the lists will also reflect input from the Pediatric Subcommittee of ODAC.

- The second mechanism is a transparent nomination process open to sponsors and academic investigators to occur during or prior to meetings of the Pediatric Subcommittee of the ODAC.

- The third proposed mechanism is for clinical investigators or sponsors to request a meeting with the FDA to discuss new scientific data related to a new or existing molecular target which may warrant a change in that target's status as relevant or non-relevant.

Information from these sources could then be assessed by the FDA, with input from the Pediatric Subcommittee of the ODAC, to determine whether there is sufficient new evidence to support changing the relevance status of the target of interest.

Additional factors that may require consideration when seeking to utilize the list of molecular targets for decisions regarding pediatric evaluation include analysis of clinical benefit and risk, the availability of pediatric formulations, and the adequacy of patient populations when planning clinical trials. These factors may vary with each targeted product under consideration for pediatric study and will be assessed and subject to multi-stakeholder discussion.

The preliminary list of relevant and non-relevant targets (attached) has been constructed in collaboration with the NCI and with input from recognized, multi-disciplinary experts in translational and clinical research in pediatric cancer from academia and the pharmaceutical industry. The FDA welcomes discussion of the proposed lists and input on the additional considerations and factors to guide pediatric clinical investigations with the expectation of expediting the development of safe and effective therapies for children with cancer.