FDA Briefing Document
Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

May 12, 2021

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package will not include issues relevant to any final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

The subcommittee will discuss real-world evidence (RWE) for regulatory use in pediatrics, real-world data (RWD) resources, and RWD and RWE to advance pediatric safety assessments of oncology drug products in children within the context of the FDA Framework for RWE. Potential data sources and publicly available platforms including those made possible through the development and implementation of the National Cancer Institute's Childhood Cancer Data Initiative will be discussed. The potential for use of data sources to construct external controls to evaluate effectiveness of investigational products will be considered given the frequent dependence on single-arm studies due to extremely small study populations, now exaggerated by molecularly defined subtypes of the rare cancer types that occur in children.

The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Memorandum

Date: April 23, 2021

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Gregory Reaman, MD
Associate Director for Pediatric Oncology, Oncology Center of Excellence, Office of the Commissioner, FDA

Subject: FDA Background Package for May 12, 2021 Meeting

Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC meeting. The Subcommittee will consider the current state of the resources of real world data in pediatric oncology and the expanding efforts of the National Cancer Institute's Childhood Cancer Data Initiative (CCDI) in aggregating and integrating demographic, biologic, including but not limited to detailed genomic and proteomic tumor characterization at diagnosis and relapse, and clinical outcome data. Discussions will focus on how CCDI might create a resource of potential Real World Data (RWD) to generate appropriate Real World Evidence (RWE) for possible use in various pediatric cancer drug development efforts.

As always, we appreciate your time and commitment and look forward to an informative meeting on May 12, 2021.

Real-world evidence (RWE) for regulatory use in pediatrics, real-world data (RWD) resources, and RWD and RWE to advance pediatric safety assessments of oncology drug products in children within the context of the FDA Framework for RWE

The particular matter for this meeting will be review and discussion of potential uses of Real World Data (RWD) and Real World Evidence (RWE) in Pediatric Drug Development.
The use of RWD is a key strategic priority for the FDA. In alignment with the 21st Century Cures Act, the FDA is evaluating trial design and evidence development modernization using RWD to support or satisfy drug post approval study requirements pursuant to the Act as well as supporting the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act. The FDA Framework for Real-World Evidence establishes a clear foundation for the use of RWD in regulatory decision making; however, there is a need to enhance understanding of the appropriate potential applications of fit-for-purpose RWD for regulatory objectives.

This may include advanced data characteriziation to establish the RWD validity, assessment of study design and cohort selection, use of appropriate statistical methodologies, and validation of real world (RW) endpoints (including traditional efficacy endpoint surrogates and PROs collected outside clinical trials) in answering a specific clinical question to support regulatory decision making. Pediatric oncology is a therapeutic area that may benefit from the potential uses of RWD in the context of evidence development moderinization to improve the efficiency of the clinical research process in enabling earlier access for patients to effective therapies in areas of high need.

In addition to the potential use of RWD and RWE in regulatory decision-making related to effectiveness, an opportunity exists to facilitate and expand the post-marketing safety assessment of new cancer drugs in children. This is of particular importance given the duration of exposure to most cancer therapies and the length of time to fully accrue to clinical trials and provide sufficient follow-up to evaluate both effectiveness and initial safety of cancer products approved for use in children. As well, given the broad age range of children afflicted with cancer, neonates through adolescence, particular developmental toxicities may not be apparent until years after conclusion of therapy. Given the nearly unparalleled commitment to long term follow-up and survivorship research that is integral to childhood cancer clinical and translational research, appropriately purposed RWD may add to RWE in further informing the both short and long term toxicity of new cancer agents in children.

Real world data (RWD) from children and adolescents with cancer may be sourced from controlled clinical trial results, registries, expanded access experience with investigational and off label use experience of approved cancer therapies. The potential for use of well characterized and appropriately standardized data to create sufficient evidence is of particular interest to pediatric cancer drug development in light of the rarity of cancer in general, in the specific types of cancer, and in molecularly phenotyped subtypes of the cancers that occur in children. Rarity

of the disease in children creates issues with small study populations for clinical trials designed to demonstrate effectiveness as well as sufficient numbers of treated patients on studies for appropriate evaluation of both short and long-term safety. Due to the paucity of patient numbers, clinical trials of new cancer drugs in children are frequently designed as single arm trials with plans to use historical or external controls as a comparator to demonstrate effectiveness in marketing applications. RWE can also contribute to the development of priors for randomized studies incorporating adaptive Bayesian designs.

The availability of reliable sources of real world data is pivotal to the potential of creating adequate RWE to construct appropriate external controls. The potential use of RWE in regulatory decision-making will be discussed in accordance with the recently published FDA Framework on RWE. The 21st Century Cures Act, passed in 2016, prompted a focus by the FDA on RWD and RWE and their potential use in regulatory decision-making by addressing evidence gaps and informing the "totality of evidence" when evaluating the safety and effectiveness of new drugs. RWE has been used by FDA to monitor post-market safety and adverse event experience, by health care providers and payors to support coverage decisions, and by clinical investigators and drug manufacturers to inform clinical trial designs for evaluation of new treatment approaches.

RWD relate to an indidual or collective patient health status or delivery of health care collected from various sources including: electronic health records, billing and insurance claims data, registries, and patient-generated data. The use of computers, mobile devices and wearables has expanded opportunities to generate real world data to both better design trials and to guide development and approval of new therapeutic products following analysis of data generated. Expanding access to reliable sources of real world data has enabled the optimal use of medical products in the real-world practice setting. This has contributed to a new "totality of evidence" that can more broadly inform safe and effective use of products in a real-world, diverse patient population, building on the typical data sets derived from the tightly defined eligibility criteria governing enrollment on controlled clinical trials of highly enriched, homogeneous patient populations.

The Framework for FDA's Real World Evidence Program was published in 2018 and provides accepted definitions of RWD and RWE and the scope of FDA's RWE Program. (See Appendix) The 21st Century Cures Act (Cures Act) was signed into law on December 13, 2016 and was designed to accelerate medical product development and bring new innovations and advances more rapidly and efficiently to the patients who need them. The Cures Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA has created a framework for evaluating the potential use of real-world evidence (RWE) to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy post-approval study requirements of a new drug. The program extends also to biologic products licensed under section 351 of the Public Health Service Act. The RWE Program includes demonstration projects, stakeholder engagement, processes to ensure senior leadership input into evaluation of RWE, and promotion of shared learning and consistency in use of the framework, and guidance documents to assist developers of new medicinal products. RWD can be used to improve the efficiency of clinical trials even when not used to generate RWE to support a product's effectiveness. Examples include: hypothesis generation for randomized

controlled trials (RCT) development, identification of drug development tools such as biomarkers, assessment of study feasibility in the context of planned eligibility criteria and study site considerations, information on prior probability distributions for Bayesian designs, identification of prognostic variables and baseline characteristics for stratification or enrichment strategies, and development of geographically distributed research cohorts.

FDA also has a long and extensive history of using RWE to monitor drug safety post-approval, the Sentinel System, as well as multiple collaborative pharmacoepidemiologic studies. Outside of the evaluation of comparative effectiveness of some vaccines, the use of RWE to support effectiveness determinations is much more limited and currently confined to approvals of products for rare and/or life-threatening diseases such as cancer.

Key considerations for the acceptance of trials or studies with RWD/RWE to support effectiveness decisions include whether the RWD are fit for use, whether the trial or study design used to generate RWE can provide adequate scientific evidence to help address a regulatory question, and whether the study conduct meets regulatory requirements for data standards, collection, and integrity and study monitoting. These three elements are planned to be used to evaluate individual supplemental applications and more generally to guide the FDA's RWE Program.

Another effort of the FDA RWD/RWE Program will focus on addressing the gaps in RWD sources given the difficulties in obtaining all necessary data from current electronic health records (EHRs) and insurance claims forms including the investigation of mobile technologies, electronic patient reported outcome tools, wearanbles, and biosensors. Another important effort includes addressing the challenge of integrating various data sources that contribute information on a given patient and the requirement for a unique patient identifier.

The Program plans to explore the potential for study designs using RWD to support effectiveness including randomized designs, non-randomized, single arm trials with external controls, and observational studies.

The use of RWD and RWE in supporting decisions related to effectiveness is not its only potential application to new drug development for children with cancer As a result of several pediatric legislative initiatives over the past two decades, results of multiple pediatric clinical trials of new drugs have provided important information regarding both effectiveness and safety to product labeling. Both the Best Pharmaceuticals for Children (BPCA) and the Pediatric Research Equity Act (PREA), passed in 2002 and 2003 respectively also require the FDA to review case reports of adverse events associated with the use of medical products studied in children under these two pieces of legislation. Ths review process, conducted by the FDA's Pediatric Advisory Committee (PAC) contributes to the general knowledge of medical product safety in children. However, the full range of safety issues and concerns cannot be gleaned from case reports of adverse events (AEs) alone as the attribution of a drug product to the safety concern is difficult and sometimes impossible. The methodological difficulties are compounded by the fact that some AEs may occur long after treatment which is especially problematic in the case of AEs on growth and development.

An essential challenge to studying drug safety in children, especially those safety concerns with a long latency period is establishing associations between exposure and critical developmental time periods and the longitudinal nature of required studies. As well, drug-associated adverse events that may be uncommon in adults may be even less common in children and unique drug-associated AEs in children may be rare and unlikely to be detected. Collection of data from large numbers of children is required to investigate certain specific safety issues and may well require multiple different data sources. The detection of safety signals requiring long latency periods are especially difficulty as the routine sources of data are compromised by the migratory nature of children for one health care institution and/or provider to another as they age and changes in insurance providers Although pediatric oncology has a long track record of integrating clinical management and clinical research with clinical trials that incorporate longitudinal follow up, the focus of follow up is treatment outcome and duration of response to therapy rather than emergence of AEs. Long term follow up utilized in specific survivorship research efforts, clearly focused on existing and emergent long term toxicities has occasionally provided data on specific toxicities attributable to specific drug products. Opportunities to leverage RWD from long term follow up of successfully treated childhood cancer patients to provide RWE of long term drug safety require exploration. Although RWE has not been fully applied to address questions of medication safety in children, the emerging sources of data from clinical trial and observational studies in pediatric oncology, especially those incorporating lenthy longitudinal follow up might provide opportunities for more efficient and accurate intermediate and long term safety data of cancer drugs approved for use in children.

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7. Framework for FDA's Real-World Evidence Program

   https://www.fda.gov/media/120060/download

Discussion of potential uses of Real World Data (RWD) and Real World Evidence (RWE) in Pediatric Drug Development

1. Consider the potential of existing and future RWD resources that may provide RWE to support pediatric cancer drug development programs. Consider potential uses to inform regulatory decision-making. Consider specific pediatric cancer drug development programs that might benefit.

2. Given the discussion of the FDA framework on the use of RWD and RWE on regulatory decision-making, consider how best to assess the appropriateness of existing or emerging data sources as potential sources of RWD. Discuss critical attributes of such data.

3. Consider the real and perceived limitations to RWE from existing and developing registries in pediatric cancer drug development as a result of the General Patient Data Regulations (GPDR) in the European Union.

4. Consider possible mechanisms for how and by whom attribution of RWD/RWE- generated AEs of new cancer drugs can be accomplished, and data optimally aggregated to inform patients and providers.