

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Working Group Conference Call
August 14, 2018
11:00 a.m.–11:25 a.m. ET**

Participants

Peter Adamson, M.D.
Najat Bouchkouj, M.D.
Diana Bradford, M.D.
Gilbert Burckart, Pharm.D.
Patricia Dinndorf, M.D.
Steven Dubois, M.D.
Ira Dunkel, M.D.
Lori Ehrlich, M.D.
E. Anders Kolb, M.D.
Kate Matthay, M.D.
Kathleen Neville, M.D., M.S.
Julie Park, M.D.
Gregory Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Malcolm Smith, M.D.
Perdita Taylor-Zapata, M.D.
Anne Zajicek, M.D., Pharm.D.

Purpose

The purpose of this call was to discuss the following:

- Implementation of the FDA Reauthorization Act (FDARA) 2017
- List of relevant molecular targets
- Potential products for discussion by the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

Implementating FDARA 2017 Provisions

Dr. Reaman began by noting that while most participants likely were familiar with most of the information that he planned to present, some of this information might be new to other call participants. Therefore, he presented a brief review of the U.S. Food and Drug Administration (FDA) planned actions to implement new and/or revised provisions to FDARA 2017, in particular changes resulting from amendments to the Pediatric Research Equity Act (PREA), a component of FDARA. Dr. Reaman explained that the Research to Accelerate Cures and Equity (RACE) for Children Act of 2017 updates PREA. He further noted that these amendments were enacted because legislative initiatives that support pediatric drug development—notably, the Best Pharmaceuticals for Children Act (BPCA) and PREA— seem to have had less impact in

incentivizing drug studies in oncology than in other clinical areas. To date, no oncology drug has triggered PREA oversight.

Dr. Reaman briefly reviewed key elements of PREA compared with BPCA. He pointed out that while PREA requires mandatory studies; those studies are based on indications, whereas BPCA supports voluntary studies with incentives. In addition, until now, under PREA, orphan indications have been exempt. Under the RACE for Children Act, the FDA must now require pediatric assessments when molecular targets of drugs under FDA review are substantially relevant to pediatric cancers.

Dr. Reaman emphasized that the elimination of the orphan exemption for pediatric studies for cancer drugs is a major change resulting in a number of subsequent actions. In addition, under FDARA 2017, the FDA is now required to develop, maintain, and publish a list of “relevant” molecular targets. He noted that the intent is to keep the definition of molecular targets broad, to ensure regulatory flexibility without limiting FDA authority. FDA has been working with the National Cancer Institute (NCI) and other constituent agencies, to maintain and develop processes for regularly updating the molecular targets list, currently posted on the FDA/Oncology Center of Excellence (OCE) website. Under FDARA 2017, the FDA also is mandated to convene open public meetings to elicit additions to the list. Dr. Reaman noted that the FDA already has conducted several public meetings, the most recent during the Pediatric Subcommittee of ODAC meeting in June 2018. He explained that during that meeting, participants discussed considerations for application of the target lists, as well as processes for prioritizing these agents. Participants also discussed processes for fostering international collaboration/coordination to avoid, or minimize duplication of effort or confusion among domestic and international health agencies.

Dr. Reaman explained that no regulatory decisions have been finalized as yet. At this time, the emphasis is on accelerating appropriate initial pediatric evaluations, rather than on increasing the number of pediatric Phase 1 studies. He explained that the FDA is alerting sponsors of these new conditions and requirements, and that an initial pediatric study plan must be submitted before submission of a New Drug Application.

He noted that the FDA is considering options for fostering scientific discussion among internal and external stakeholders, including expanding monthly international cluster calls, as well as international strategy forums. He mentioned that the FDA had opened a *Federal Register* public docket to invite comment from the public, as well as from sponsors on additions to or deletions from the published lists. Dr. Reaman also noted that the Agency is assessing ways to establish a framework to define and classify pediatric “relevance” for current and future molecular targets.

Potential Products for Discussion by the Pediatric Subcommittee of the ODAC

Dr. Reaman next asked call participants for their input regarding products that they would recommend for presentation and discussion at upcoming sessions of the Pediatric Subcommittee of the ODAC. He noted that BXQ-350, sponsored by Bexion Pharmaceuticals, presents some encouraging results that might warrant further discussion. Dr. Reaman explained that the product

which is a nanovesicle containing saposin targets phosphatidyl serine domains of tumor cells; the drug sponsors submitted a development plan that focuses on application to glioblastomas and other high-grade gliomas. Also, studies of this product are in the early stages, currently Phase 1 studies in adults. Dr. Reaman suggested that while the initial development plan submission focused on brain tumors, there are other areas that perhaps should be explored. He also noted out that the sponsor had submitted a proposed pediatric study request that did not meet submission criteria, which he suggested might be a reflection of the sponsor's lack of experience in pediatric drug programs.

He suggested that a company such as this might be helped by having a discussion with, and getting input from, this Working Group and other members of the investigator community. Dr. Reaman asked participants for their opinion on whether to invite this sponsor to present at the next ODAC meeting, most likely June 2019.

Dr. Dubois asked if Bexion had developed a responder hypothesis. Dr. Reaman acknowledged that it is still early in the process, but that the sponsor might be helped in formulating a study hypothesis using input from the Working Group comments.

Dr. Park asked if *in vitro* studies had been conducted. Dr. Reaman noted that both *in vitro* and *in vivo* animal model data had been collected but those data were limited mainly to glioblastomas.

Dr. Smith inquired if any data had been published to date. Dr. Reaman noted that the sponsor is currently recruiting patients for adult Phase 1, and was not aware of any updates on clinical trials.

Dr. Reaman again noted that the mechanism of action of this agent is very novel. He also pointed out that this agent is not on the target list, but explained that inclusion on the target list is not a requirement for pediatric evaluations. He pointed out that the sponsor was interested in exploring the potential for appropriate pediatric indication.

Call participants agreed to continue plan on inviting Bexion to present at the next Pediatric Subcommittee on ODAC meeting.

Follow up Discussion/Other Products of Interest

Dr. Reaman asked participants to discuss any other potential products that they would recommend for ODAC meeting presentations. At this time, no other suggestions were offered.

Dr. Reaman closed the meeting by noting that he would keep Working Group members updated on further discussion and communication with Bexion.

Action Items

In addition to the primary target lists that Dr. Reaman had sent to call participants, he will send them the link to the current FDA/OCE website.