Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Core Working Group Conference Call
April 9, 2012
12:00 p.m.–12:55 p.m. ET

Participants

Peter C. Adamson, M.D.
Lisa Mathis, M.D.
Gregory H. Reaman, M.D.
Malcolm Smith, M.D., Ph.D.
Perdita Taylor-Zapata, M.D.

Objective of Working Group

There have been many advances in treating pediatric cancers despite the fact that many currently utilized drugs are used off label and there is a relative dearth of new drugs approved for pediatric indications. This working group was established to provide a forum for regular exchange of ideas between pediatric oncology practice and research experts and regulators.

Agenda

The agenda was as follows:

- Introductions
- Future topics of discussion, such as
  - Sharing information about drugs in early phases of development and how to issue Written Requests (WRs) for such products early in development
  - How to share information that may be confidential
  - Ideas for additional working group members
  - Possible work products of the working group
- Frequency of meetings and need for face-to-face meetings.

Introductions

- Dr. Mathis is a member of the Pediatric and Maternal Health staff in the Office of New Drugs, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA). She oversees pediatric drug development at CDER.
- Dr. Adamson is at the Children's Hospital of Philadelphia. He is chair of the Children's Oncology Group (COG).
- Dr. Smith is in the Cancer Therapy Evaluation Program at the National Cancer Institute. He is the program director of COG, the COG phase 1 consortium, and the preclinical testing program.

- Dr. Taylor-Zapata is with the Obstetric and Pediatric Pharmacology Branch, Center for Research for Mothers and Children, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.
- Dr. Reaman is associate director of the Office of Hematology and Oncology Product, CDER, FDA.

Future Topics of Discussion

Dr. Mathis explained that the impetus for starting this working group was the reauthorization of BPCA and the Pediatric Research Equity Act (PREA), the timing of Dr. Reaman joining the FDA, and new efforts to maximize work under BPCA and PREA. Dr. Mathis' role is to facilitate communication between investigators and the FDA. Working group members will serve as subject matter experts to determine what the working group can do for the BPCA program. Dr. Adamson previously communicated with the FDA about focusing on products that are in the early phase of development. Historically, the FDA has issued WRs for studies conducted by COG and already published. Drug sponsors submit existing data, rather than the FDA asking for drug studies early in the development phase. Dr. Adamson noted that the FDA is missing opportunities to conduct studies on some drug products and maximize data collection. There were some concerns that working group discussions about drugs in development may prohibit existing working group members from conducting their own research due to conflicts of interest. This is an area that requires clarification in the future.

Sharing Information about Drugs in Early Phases of Development and How to Issue WRs for Such Products Early in Development. Dr. Adamson asked about the limitations under BPCA, specifically, when a WR can be issued, whether it can be issued before a New Drug Application (NDA), what happens if a WR is issued and rejected, and whether a WR could be reissued. Dr. Mathis explained that WRs can be issued for pediatric studies as soon as there are sufficient data to conduct such studies. A WR can be issued for an Investigational New Drug (IND) product at any time during the development process, even as early as phase 1. The WR must include a clinical trial in the pediatric population and can include animal studies and adult studies if they relate to the pediatric drug development.

If a WR is issued and the drug sponsor rejects it, the WR can be referred to the National Institutes of Health (NIH). The study can be conducted by the NIH or the drug sponsor can be forced to conduct the study under PREA. Even if the drug is an IND or is on-patent, the NIH can conduct the study. Dr. Reaman noted that there is flexibility in when a WR can be issued. Information from the pediatric investigative community is not required, but information and early expression of interest from the pediatric investigator community would greatly facilitate the process. Often there is already some communication between investigators and the drug company. The drug company can submit a Proposed Pediatric Study Request (PPSR), which can trigger a WR. The PPSR can be submitted before the pre-IND meeting.

For WRs for on-patent drugs, a PREA mechanism can force drug sponsors to conduct studies, particularly if there is a strong public health benefit, and even for an off-label indication. However, this mechanism has not been used because there has been no need to do so. This

mechanism could be used if the number of rejected WRs increases due to WRs issued earlier development process. A WR will not be reissued if the study is conducted by the NIH or the company is forced to conduct a study under PREA. Another PPSR could be submitted if the drug is for a different indication or population. Currently, many new oncology drugs get waivers under PREA because they receive orphan designation. Given the focus on development of personalized medicines, this situation will likely increase. However, the goal is to move up the timeline for early-phase studies.

Dr. Taylor-Zapata explained that the NIH has conducted a few studies of on-patent drugs. The NIH Foundation provided funding for one of these studies. Drugs for these studies are generally purchased from the drug companies. The drug companies must be notified if the drug is an IND or must agree if the drug is not yet on the market. The companies allow the IND to be cross-referenced before the NDA. WRs have been issued before an NDA for different pediatric indications but not for oncology. About 10 percent of WRs are for INDs (that is, before an NDA for any indication).

For drug companies, locking in exclusivity early could be beneficial for well-targeted pediatric drugs with a good probability of approval. Most of the exclusivity that has been granted has been for phase 1 or phase 2 studies alone, where the drug does not yet have a pediatric indication. Drugs companies would be expected to conduct a definitive study if the drug has a strong signal of activity. There is an opportunity to redefine definitive studies. They do not necessarily have to be large, randomized phase 3 studies. Another opportunity is using more surrogate endpoints for screening high-risk populations in phase 2 studies.

Dr. Mathis asked whether the working group's regular communications would help advance studies of pediatric oncology products. One issue is having data that will trigger discussions and integrating outside information with FDA information. Having appropriate information would help the FDA and investigators raise the issue of companies developing pediatric plans for drugs in the investigational phase.

How To Share Information that May Be Confidential. One of the challenges of sharing information is dealing with different companies that may have drugs in relatively similar stages of development. The challenges include data confidentiality and issues of exclusivity. It may be difficult to develop a regulatory framework that addresses these challenges. It may be better to address them on an individual, situational basis, with investigators providing decision-making input to the FDA. There should be no perception of conflict of interest. The FDA's Pediatric Review Board and Exclusivity Board may have to consider multiple WRs and definitive studies that cannot be conducted by one company with one product.

Ideas for Additional Working Group Members. Drs. Adamson, Reaman, and Smith agreed to form a group of five or six people from COG to develop a list of nominees. Dr. Taylor-Zapata explained that previous BPCA working groups have had 15–20 members. Dr. Reaman proposed having a smaller group, with various subject matter experts serving as temporary members as their expertise is needed (for example, depending on the drug and specific indications).

Possible Work Products. Dr. Mathis asked for ideas for possible work products. The FDA has a draft guidance that will be finalized after additional information is received. Dr. Reaman proposed a white paper, which could then be used to inform the FDA guidance. The white paper should be drafted once two or three WRs have been issued for drugs in the IND phase. Another option is for the working group to play a role in editing or commenting on an FDA annual report on oncology drugs in early development. Such an annual report could be published in a pediatric journal, which would provide greater visibility and transparency. Dr. Reaman noted that about half of the approvals for oncology indications since January 2010 had orphan designations, which would not trigger the PREA mechanism. The working group could draft a pediatric-specific report explaining why there were no pediatric development plans for these drugs. The working group's communications should be directed at key researchers and the pharmaceutical industry.

Frequency of Meetings and Need for Face-to-Face Meetings

These topics were not discussed.

Summary

Dr. Mathis summarized the conference call as follows:

- The working group discussed different ways to share information. The working group will begin by addressing pediatric oncology drug development earlier in the development process, specifically the IND phase.
- The working group discussed BPCA and PREA. The section of PREA that deals with on-patent drugs (that is, referral if pediatric studies are not completed) was distributed to the group. Although the PREA mechanism has never been used because no WR for an on-patent drug has been rejected, this mechanism should be kept in mind for pediatric oncology drugs.
- The working group discussed ways to share confidential information. The working group will determine best approaches when the issue arises.
- Working group members should consider additional working group members and alternates for current members.
- A possible work product is a white paper. In an effort to increase transparency, the working group should consider other work products.

Action Items:

- Drs. Adamson and Smith will develop a list of additional core group members and contributing subject matter experts.
- Nominations for additional working group members and alternates should be sent to Brandy Weathersby at Circle Solutions.
- Circle Solutions will poll working group members to determine the best time for the next conference call.