

**Best Pharmaceuticals for Children Act (BPCA)
Dermatology Therapeutic Area Working Group Conference Call and Webinar
January 30, 2014
10:00 a.m.–11:00 a.m. ET**

Participants

Chair

Elaine Siegfried, M.D.

Members

Carl C. Baker, M.D., Ph.D.
Julie Block
Beth Drolet, M.D.
Lawrence F. Eichenfield, M.D.
Roselyn Epps, M.D.
Adelaide Hebert, M.D.
Thomas Hultsch, M.D., Ph.D.
Marie Ann Leyko, Ph.D.
Zhaoxia Ren, M.D., Ph.D.
Alex Silver
Perdita Taylor-Zapata, M.D.
Kelly Wade, M.D., Ph.D.
Anne Zajicek, M.D., Pharm.D.

Food and Drug Administration (FDA)

Denise Cook, M.D.
Lori Gorski
Alyson Karesh, M.D.
M. Dianne Murphy, M.D.
William Rodriguez, M.D., Ph.D.
Donna Snyder, M.D.

Purpose

The purpose of the call and webinar was for the U.S. Food and Drug Administration (FDA) to provide feedback to the 2012 BPCA Dermatology Therapeutic Area Working Group about their submitted recommendations to the National Institutes of Health (NIH) BPCA Program.

Greetings

Dr. Taylor-Zapata thanked the participants for their continued interest in the BPCA Program. She noted that in the past, there has not been a mechanism for the FDA to provide feedback to BPCA working groups, and this call represents a new opportunity.

The BPCA: Perspectives from the NIH

Dr. Zajicek explained that Congress passed the BPCA in 2002 and reauthorized it in 2007 and 2012. Because the pharmaceutical industry does not have an incentive to study off-patent drugs for pediatric labeling, the legislation requests that the NIH do three things: prioritize drugs (and therapeutic areas, starting in 2007), conduct trials, and submit the data to the FDA.

For prioritization, the legislation instructs the NIH to consider availability of safety and efficacy data, the need for additional data, whether additional studies would produce health benefits, and whether the drug needs reformulation. When considering health benefits, the NIH prioritizes both severe conditions, such as cancer, and conditions that occur frequently, such as asthma.

In 2007 and 2012, Congress amended the law to instruct the NIH to consider therapeutic gaps, potential health benefits of research, and adequacy of the necessary infrastructure for research. These changes raised the issue of the lack of pediatric clinical pharmacologists available to perform studies. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) added T32 programs in pediatric clinical pharmacology and created a master contract for performing BPCA studies.

Consultation with pediatric experts is part of the prioritization process. Dr. Zajicek presented a list of prioritized therapeutic areas. After prioritization, the NIH may submit a Proposed Pediatric Study Request/Written Request to the FDA. The NIH serves as the sponsor, publishing data and submitting data to the FDA.

Dr. Murphy explained that since 2007, any studies conducted under the BPCA and submitted to the FDA will result in a labeling change. This means the results of the studies, irrespective of whether or not they provided a new indication for pediatrics, will be added to the label. Even negative information can be very informative and useful to others. When studies are submitted via the NIH to the FDA docket, there is a strict deadline for the FDA to negotiate what information will be included in the label with the sponsor who owns the label.

Dr. Zajicek reviewed the clinical trials completed under individual contracts before the Pediatric Trials Network (PTN) was in place, including a trial that led to a recent labeling change for nitroprusside. The PTN initially focused on neonates, because the 2012 BPCA legislation mentioned the lack of labeling for that group, and antimicrobials. The PTN is also working on opportunistic protocols, which are small pharmacokinetics and safety studies.

Limitations for the BPCA Program include:

- Funding—Congress did not appropriate new funds. The NICHD and about 21 other NIH Institutes and Centers contribute funding.
- Drug supply and affordability—The BPCA Program has received requests to study biologics but cannot afford such studies.
- Access to patients—The PTN cannot study drugs that are not used frequently in patients at the 40 to 50 PTN sites.

- Black box warnings—The BPCA Program would probably not move ahead with a study of a drug that had a black box warning.

The NIH submits de-identified data to the FDA docket; these data are publically available. The FDA negotiates the label change with the drug manufacturer within 180 days after the data are submitted to the docket. On January 24, 2014, the *Federal Register* published the announcement of the labeling change for nitroprusside.

Dr. Zajicek presented a list of funding announcements for the NICHD Obstetric and Pediatric Pharmacology and Therapeutics Branch. The call participants could use these mechanisms to fund projects that do not fit within the BPCA Program. The NICHD does not require preauthorization to submit clinical trial concepts.

Dr. Zajicek presented a map of PTN sites and said that participants could contact the PTN at <https://pediatrictrials.org/contact-info> for information about becoming a PTN site.

She thanked the group for its concept sheet on infantile hemangioma; this project is likely to move forward in 2014.

The slides for this presentation are available at http://bpcanichd.nih.gov/prioritization/working_groups/Documents/BPCA_Perspectives_Zajicek.pdf.

FDA Feedback on Working Group Recommendations

Dr. Snyder said she was pleased with the recent labeling change for nitroprusside.

The FDA has two mechanisms to obtain pediatric labeling:

- The Pediatric Research Equity Act (PREA), passed in 1999, which requires companies to assess safety and effectiveness of new drugs/biologics
- The BPCA, which provides a financial incentive for companies to conduct studies and allows the NIH to conduct studies if companies decline.

Many drugs approved before the PREA was passed are used off label in pediatrics and may be candidates for NIH study. To add pediatric information to a drug label, the FDA requires dosing, safety, and efficacy data. Efficacy may be extrapolated from adults or between pediatric populations, depending on the disease pathology and likely response to treatment.

The FDA can advise the NIH on what studies would be needed to add a pediatric indication to labeling. Depending on the drug and indication, a full developmental program may be needed, including formulation development, dosing, and safety and efficacy data. The FDA can advise on the feasibility of the program. The FDA cannot provide information on current drug development programs but can direct the NIH to publicly available information.

Dr. Snyder thanked the group for its recommendations and noted that this conference call would be limited to specific drugs and biologic products. Other recommendations were sent to the appropriate organizations within the FDA.

Dr. Cook noted that this working group was tasked with identifying drugs and indications that could be studied under the BPCA. The group identified oral and topical propranolol in hemangioma of infancy (HOI) and timolol maleate ophthalmic solution. The group recommended that studies of oral propranolol are needed for complicated HOI and for infants younger than 2 months and preterm infants. The group also recommended that studies of topical propranolol and topical timolol maleate ophthalmic solution are needed for hemangiomas with ulceration, for periorbital lesions, and for infants younger than 2 months and preterm infants.

The slides for this presentation are available at http://bpca.nichd.nih.gov/prioritization/working_groups/Documents/FDA_Feedback_PedDerm_013014.pdf.

Discussion

Dr. Siegfried commented on the limitation on studying drugs with black box warnings. The group recommended studies of topical calcineurin inhibitors (TCIs), and she was not sure why TCIs were not selected for discussion. The black box warning on TCIs has impaired access to the drug for children without other options and has created a public perception problem. The fact that TCIs are not eligible for further study is another blow. The black box warning also had an impact on drug development for atopic dermatitis, although new drugs are entering the drug development pipeline after 10 years. She asked whether the group could work with other individuals at the FDA on these issues.

Dr. Epps inquired about the communication of the final presentation of the working group to all group members. Dr. Siegfried said that the process for this working group included each subcommittee sending recommendations, and she put the final presentation together. However, the presentation could have certainly been made available to anyone who requested it prior to presentation. Dr. Taylor-Zapata said that she would recommend more communication about the final presentation in future working groups.

Dr. Epps said that the company owns the black box or the label, and the company should address this issue. Because the company does not provide all information, the group cannot determine whether the drug is safe. Dr. Hebert said that she and Dr. Siegfried recently published a paper on the implications of the black box warning on TCIs. She will forward the paper to Dr. Epps. Dr. Epps said that the black box warning is not within the parameters of the BPCA charge. She thought that the tone of the presentation was not appropriate and was not well received. Dr. Siegfried said that Dr. Taylor-Zapata provided guidance for the group that the content of the presentation was appropriate.

Dr. Siegfried said that the group had wanted feedback on a mechanism for future guidance. The black box had a negative impact on future drug development; the group wanted to minimize

further problems with drug development to address this unmet medical need. Dr. Murphy said that the FDA added the black box warning after years of discussion and analysis among the FDA, the NIH, and academia. The FDA needs data from long-term follow-up studies to remove the black box warning.

Dr. Siegfried noted that it is much easier to treat children with corticosteroids because of the cost and the lack of a black box warning, even though the use is off label. There are more long-term data for TCIs than for corticosteroids. The black box warning is a disincentive for using the product that is likely safer. Dr. Murphy said that there were enough data to add the black box; the FDA would like data that would allow removal of the black box, if it is a hindrance to care.

Dr. Drolet asked whether studies to remove the black box are too expensive or long term for the BPCA Program. Dr. Cook said that the BPCA Program is for drugs that are off patent and for which there is no other way to collect the data. Dr. Murphy said that there is another mechanism to address patented drugs, but that has not been the focus of NIH efforts.

Dr. Zajicek said that the BPCA Program could not afford a long-term safety registry. Dr. Siegfried said that there are long-term safety registries for both TCI drugs, and Protopic will be off patent in February 2014. She asked whether the BPCA Program could help get the data from these long-term registries.

Dr. Drolet said that her subgroup had included a PTN member who helped to narrow the subgroup's focus to topics within the scope of the BPCA. In the future, it would be helpful for each group to include an individual who is knowledgeable about the scope of the BPCA. Dr. Taylor-Zapata said that she agrees and has already incorporated that advice into future working group developments.

Dr. Murphy said that an on-patent drug may not be a priority for study when the NIH has prioritized so many off-patent drugs. Dr. Zajicek agreed. Dr. Drolet asked about funding for BPCA studies, and Dr. Zajicek said that all BPCA studies are funded through the PTN. Other grant mechanisms may fund other projects. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) may also provide funding for dermatology research. Dr. Baker agreed and said that he could discuss NIAMS funding opportunities with anyone who contacts him.

Dr. Baker said he was pleased that the propranolol and timolol studies were potentially moving forward. He asked about the next steps after BPCA prioritization. Dr. Taylor-Zapata said that the PTN has a mechanism called a concept sheet, which provides background information, references, and an outline of the potential studies. Concept sheets can be submitted via the PTN website. Dr. Taylor-Zapata can also put participants in touch with the contact person at the PTN. The PTN steering committee reviews concept sheets and provides feedback.

Dr. Siegfried said that Dr. Baker had been helpful to the group. The BPCA process has helped to build a more organized pediatric research network, and Dr. Zajicek's list of funding mechanisms will be helpful. When the group formulated the list of unmet needs, there were no drugs for

atopic dermatitis in the drug development pipeline; now several drugs are early in the pipeline. The group suggested developing a guidance document for future trials, which would not require funding. She asked whether there was any other mechanism for creating a guidance document.

Dr. Murphy said that she recently met with pediatric leaders in the pharmaceutical industry. They noted that the United States lacks research networks that can answer questions about products in a timely manner with data that could be submitted to the FDA. In contrast, there is a British pediatric network that works efficiently. Pharmaceutical companies are now forming their own centers of pediatric excellence and trying to develop pediatric networks. There have been issues with quality control and institutional review boards. The United States needs more pediatric research networks like the PTN that can rapidly implement trials and ensure that researchers receive recognition and funding.

Dr. Siegfried said that industry has difficulty finding sites that can conduct trials and developing protocols for pediatric trials. Dr. Murphy said that pediatric centers of excellence can help address these issues. Pediatric drug development is no longer an afterthought; NIH has helped to develop pediatric networks, and now industry is beginning to fund networks. She added that studies are no longer conducted in only one country, and trials need to be harmonized.

Action Items:

- Dr. Hebert will forward a paper on the black box warning on TCIs to Dr. Epps.
- Circle Solutions, Inc., will send the webinar slides, an example concept sheet, and meeting minutes to the group.