

**Best Pharmaceuticals for Children Act (BPCA)  
Rheumatology Therapeutic Area Working Group Conference Call and Webinar  
January 17, 2014  
10:00 a.m.–10:55 a.m. ET**

**Participants**

Mara Becker, M.D., M.S.C.E.  
Marcia Buck, Pharm.D.  
Polly Ferguson, M.D.  
Lori Gorski  
Theresa Kehoe, M.D.  
Gordon Klein, M.D., M.P.H.  
J. Steven Leeder, Pharm.D., Ph.D.  
Marie Ann Leyko, Ph.D.  
Dianne Murphy, M.D.  
Rosemarie Neuner, M.D., M.P.H.  
Ronald Portman, M.D.  
Michael Reed, Pharm.D.  
Laura Schanberg, M.D.  
Douglas Silverstein, M.D.  
Donna Snyder, M.D.  
Janice Sullivan, M.D.  
Perdita Taylor-Zapata, M.D.  
Carolyn Yancey, M.D.

**Purpose**

The purpose of the call was to present and discuss the U.S. Food and Drug Administration's (FDA's) feedback on the Rheumatology Therapeutic Area Working Group's recommendations.

**Welcome**

Dr. Taylor-Zapata welcomed participants and thanked them for their involvement in the working group. For the BPCA Program, the National Institutes of Health (NIH) develops a priority list of pediatric drugs that require further study and sponsors clinical trials of priority drugs. Each year, the BPCA Program identifies two or three pediatric therapeutic areas and convenes expert working groups to discuss therapeutic needs and areas needing further study. In 2012, the therapeutic areas were dermatology and rheumatology. The working groups identified the needs for their respective areas and presented their recommendations to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the annual BPCA meeting. Until now, feedback was not given on the working groups' recommendations. Dr. Lynne Yao, Dr. Snyder, and Ms. Gorski helped develop the new mechanism for providing FDA feedback.

A slide presentation on the BPCA process—including prioritized therapeutic areas, clinical trials completed, data submission process, and funding opportunity announcements—is available at [http://bpcanichd.nih.gov/prioritization/working\\_groups/Documents/BPCA\\_Perspectives\\_Zajicek.pdf](http://bpcanichd.nih.gov/prioritization/working_groups/Documents/BPCA_Perspectives_Zajicek.pdf).

## **FDA Feedback on Working Group Recommendations Presentation**

Dr. Snyder discussed the following:

- Background information on the Pediatric Research Equity Act (PREA) and BPCA
- How the BPCA Program factors into U.S. pediatric drug development
- Considerations for labeling a drug for a pediatric indication
- FDA feedback to the NIH.

Dr. Snyder explained that the feedback is limited to specific drugs and biologic products, not therapeutic areas. Other working group recommendations that fall under the FDA's purview but are not related to specific products will be reviewed by the appropriate organizations within the FDA. Dr. Snyder reviewed the recommendations and feedback for uveitis and bone biology.

**Uveitis.** The Division of Transplant and Ophthalmology Products reviewed the recommendations on uveitis. The Division agreed that methotrexate, one of the drugs recommended for study by the working group, would be a good drug for the NIH to study. Methotrexate was approved in the 1950s and has a large safety database that could be used to support labeling. One well-controlled pharmacokinetics, safety, and efficacy study of 100–200 patients might be sufficient to collect the needed data. However, the protocol would need to clearly define the population of patients with uveitis in order to have sufficient patients to study and to collect meaningful data.

**Bone Biology.** The Bone Biology Subcommittee recommended a trial of intravenous bisphosphonate therapy in pediatric patients who require treatment with glucocorticoids for more than 6 months. A general consideration for such a pediatric trial is that the potential benefit from treatment would need to be greater than the potential risks. In the case of bisphosphonates in particular, the FDA does not believe there is greater benefit than risk. Prior experience with pediatric bisphosphonate therapy does not encourage further study. Dr. Snyder cited a study of zoledronic acid treatment for pediatric patients with severe osteogenesis imperfecta as an example.

Dr. Neuner reviewed the recommendations and feedback for pediatric systemic lupus erythematosus (SLE) and systemic juvenile idiopathic arthritis (SJIA).

**Pediatric SLE.** Currently, there are no approved treatments for lupus nephritis or neuropsychiatric lupus in adults or children. There is a lack of validated clinical endpoints for both of these manifestations. The FDA is encouraging continued research and collaborative efforts to identify endpoints and therapies that may be both safe and efficacious in treating these manifestations.

**SJIA.** In April 2013, canakinumab (Ilaris), an IL1- $\beta$  blocking agent, was approved as a treatment in patients 2 years or older with SJIA at a dose of 4 mg/kg via subcutaneous injection every 4 weeks. Cases of macrophage activation syndrome were observed in pediatric clinical studies supporting approval of this drug. Other safety concerns, which were the same as those in adults, included serious infections, neutropenia, thrombocytopenia, and severe injection site reactions.

The slides for this presentation are available at [http://bpca.nichd.nih.gov/prioritization/working\\_groups/Documents/FDA\\_Feedback\\_Rheum\\_011714.pdf](http://bpca.nichd.nih.gov/prioritization/working_groups/Documents/FDA_Feedback_Rheum_011714.pdf).

## Discussion

Dr. Klein (a member of the Bone Biology Subcommittee) asked whether the FDA's feedback on bisphosphonate therapy is definitive—that is, the FDA is not encouraging further research in this area, with the implication that the NIH will not fund any additional studies. Dr. Kehoe explained that the FDA's approach to therapy for pediatric osteoporosis-type indications is that there must be a clear potential for the benefit to outweigh the risk. For glucocorticoid-induced osteoporosis in children, the fracture benefit does not warrant the risk of bisphosphonate therapy. Currently, there are no data to support substantial fracture risk and the potential for benefit.

Dr. Klein noted that a closer model to glucocorticoid-induced osteoporosis in children may be bone injury, which results in systemic inflammation and endogenous glucocorticoids. Dr. Klein cited a study (published online December 18, 2013, in the *Journal of Bone and Mineral Research*) that demonstrated that single-dose intravenous pamidronate treatment prevented muscle breakdown and increased muscle fiber diameter, and possibly increased muscle strength. Bisphosphonates have anti-apoptotic and anti-resorptive properties, both of which fit the pathophysiology of glucocorticoid-induced osteoporosis. Dr. Klein said, although fracture data are lacking, research on pediatric bisphosphonate therapy should not be precluded.

Dr. Kehoe said this avenue of research may be out of the FDA's purview. She noted that pamidronate is not approved for osteoporosis therapy, and there are issues about conducting pediatric bone studies with pamidronate. Dr. Kehoe said she could not comment on bisphosphonate therapy and muscle pathophysiology.

Dr. Schanberg asked for elaboration on the FDA's feedback on the working group's pediatric rheumatology recommendations. She noted that the feedback does not discuss any medications for pediatric SLE, does not address issues about Plaquenil, and does not provide recommendations for SJIA. Although Ilaris has been approved, it is not the drug pediatric rheumatologists prefer due to its long-acting effects and uncertainties about initial SJIA diagnosis. Most pediatric rheumatologists prefer to start therapy with anakinra because dose adjustments are easier and the drug is short acting. Dr. Neuner explained that her slides were vetted within FDA and only the content she presented was approved. The FDA has no recommendations for specific drugs in pediatric rheumatology.

The need to study Plaquenil therapy for pediatric SLE has been discussed over the last several years. The FDA concurs that more clinical trials of Plaquenil for pediatric SLE could be conducted. In terms of the anti-IL1 class of drugs, when the working group made its recommendations in 2012, the Ilaris application was under FDA review and could not be discussed due to proprietary issues. Dr. Neuner said the FDA would not have issues with the NIH funding clinical trials of anakinra or rilonacept. Dr. Schanberg noted that, although more children are being treated with anakinra than Ilaris, there have been no studies of anakinra. It is unlikely that pediatric rheumatology treatment practice at disease onset is going to change. She said that the company that makes anakinra is small and will not seek a pediatric SJIA indication for the drug due to lack of funds.

Dr. Silverstein asked how the FDA could work with academicians to develop an application for anakinra. Dr. Schanberg said academicians are working with the anakinra manufacturer to design clinical studies, and they welcome guidance from the FDA on what type of study would be acceptable for an application. Dr. Snyder explained that if the rheumatology community believes studies are needed, it could discuss study plans with the NIH, which would then meet with the appropriate FDA Division. Another approach would be to work directly with the drug sponsor to develop a study plan and then meet with the appropriate FDA Division.

Dr. Becker commented that the approval of Ilaris should lead to further study of pediatric formulations of other IL1- $\beta$  blocking agents, particularly those that might be safer and better tolerated. Dr. Kehoe said there is no regulatory mechanism for the manufacturers of the other agents to conduct studies. However, there are PREA requirements for new drugs for pediatric SJIA. Dr. Murphy explained that the goal of FDA-NIH collaboration is to conduct studies of drugs that companies cannot or will not study. This process involves the FDA issuing a written request (WR) to the NIH for an off-patent drug or the NIH submitting a proposed WR that outlines the type of clinical trial that would be acceptable. After the FDA receives the WR, the appropriate Division determines whether the trial design will work. If a trial is conducted, the results would then be presented to the drug sponsor for labeling changes. This process has, so far, targeted off-patent products for which the drug sponsor turned down the WR. The process has resulted in labeling changes (for example, nitroprusside). Dr. Murphy said that if the drug sponsor responds to a WR and agrees to a study, the FDA cannot disclose the study plan.

Dr. Murphy said the FDA is sponsoring a workshop on September 22, 2014, for academicians and clinical investigators that will review the BPCA Program process, including the type of data required by the FDA and the NIH's experience with clinical trials.

Dr. Taylor-Zapata noted that the FDA's Review Division and Pediatric Division responded to the working group's recommendations, but it is not in their purview to provide specific recommendations back to the working group unless the working group presents a study design to the FDA at a type B or type C meeting. In this scenario, the FDA would provide recommendations based on the presentation. Dr. Taylor-Zapata further noted that if the working group members are interested in performing drug studies in the BPCA Program, they can work directly with pharmaceutical companies to propose studies to the FDA or they can work through the NIH's Pediatric Trials Network (PTN) by submitting a concept sheet for approval.

Dr. Leeder asked whether the PTN expects some evidence that data to be generated from a proposed trial are desired by the FDA. Dr. Murphy explained that the FDA first issues a WR to the drug sponsor. If the sponsor turns down the WR, it is issued to the NIH. The most recent BPCA legislation now allows the NIH to submit a proposed WR to the FDA. Dr. Murphy further explained that the rationale for conducting these pediatric studies is to gather evidence to change labeling. The FDA is responsible for negotiating with the drug sponsor to change the labeling based on new evidence.

Dr. Murphy said the new legislation may provide a mechanism to conduct a trial of an on-patent drug that the patent holder does not want to study for a pediatric indication.

Additional information on the PTN is available at <https://pediatrictrials.org>.

### **Concluding Remarks**

Dr. Taylor-Zapata explained that BPCA working groups' recommendations undergo an internal NIH review and secondary prioritization. In this secondary process, the NIH conducts further reviews based on key criteria to determine whether the NIH is interested in pursuing a study. The NIH may also determine that it has no interest in pursuing a proposed study. The working groups' recommendations are then vetted through the FDA and the PTN to assess whether a study is feasible and could result in a labeling change. Dr. Taylor-Zapata said the NIH is interested in the working group's proposed studies but needs to determine whether the studies can be conducted and, if so, how. If the working group members want to study a particular drug, they can submit a concept sheet to the PTN for review, referral, and recommendations. The PTN will only provide recommendations in response to a submitted concept sheet.

### **Action Item:**

- Dr. Taylor-Zapata will send the PTN link to the working group that provides information about how to develop and submit a concept sheet.