

**Best Pharmaceuticals for Children Act (BPCA)
Dermatology Therapeutic Area Working Group Conference Call and Webinar
November 5, 2012
9:30 a.m.–11:00 a.m. ET**

Participants

Chair

Elaine Siegfried, M.D.

Members

Carl C. Baker, M.D., Ph.D.
Katherine Berezny, M.P.H.
Beth Drolet, M.D.
Lawrence F. Eichenfield, M.D.
Adelaide Hebert, M.D.
Thomas Hultsch, M.D., Ph.D.
Marie Ann Leyko, Ph.D.
Hanna Phan, Pharm.D.
Alex Silver
Perdita Taylor-Zapata, M.D.
Wynnis Tom, M.D.
Jonathan K. Wilkin, M.D.
Teri Moser Woo, Ph.D., R.N.

Food and Drug Administration (FDA)

Denise Cook, M.D.
Denise J. Pica-Branco, Ph.D.

Purpose

The purpose of the call and webinar was to present the subcommittees' recommendations to the BPCA of the four areas identified as most important: genodermatosis, infantile hemangiomas, pediatric drug development issues in dermatology, and severe atopic dermatitis.

Discussion

Genodermatosis Subcommittee

Dr. Tom presented a summary of this subcommittee's recommendations. There are currently no FDA-approved therapeutic agents to treat epidermolysis bullosa (EB). Although EB trials are being conducted, such as the one on gene modulation and skin grafts at Stanford University for patients ages 16 and older, the subcommittee wants to try to get younger children included in the trials. Having earlier correction of the condition would have a bigger impact for patients; thus,

one of the aims could be to help develop parameters that would improve trial safety for younger patients. There are no FDA-approved drugs to compare, so regardless of which treatment trial comes through first, two objectives are important. The first objective is to help develop standardized outcomes measures to better assess efficacy. Severity scoring is being worked on, but additional measurements are needed. The second objective is to support validating the testing of different outcome measures, such as improvement of blistering, enhanced mobility, and better quality of life.

Dr. Baker said the National Institute of Arthritis and Musculoskeletal and Skin Diseases currently has a Request For Application out for developing and validating outcome measures. To approve including children in clinical trials, the FDA requires evidence of safety in adults and evidence of efficacy and benefit to the adult patients. For that reason, it is important to have outcome measures.

Dr. Silver said this topic is very timely because a number of potential EB trials are coming up, including protein replacement therapy and gene therapy. Anne Lucky, M.D., and her team are creating a master database, and including children is important because competing trials need to select from this relatively small patient population. The trials need to be as safe as possible, and although it is vital to get the best therapies to trial as quickly as possible, there need to be enough subjects in a specific subset of EB to conduct the trials. Many new products are available that have not been adequately tested in children, such as Keragel. Trials are needed to determine which doses are appropriate for various cases of EB. Dr. Silver hopes the field will see a lot of progress in the coming years in relation to including younger children in clinical trials.

The subcommittee supports involving children in EB trials because this condition is so ravaging to the body in its severe forms. Thus, not doing anything to treat it is paramount to a death sentence. Also, there are many upcoming trials with different approaches, and when there are multiple trials in a rare disease community, it can be difficult to find enough trial subjects. It will help increase trial sizes if younger children are allowed to participate. Dr. Siegfried asked whether this fact should be added to the committees' recommendations. A participant said perhaps the committee could recommend that children with the most severe subtypes of the disease be involved—those with junctional or recessive dystrophic EB. Dr. Silver explained that the level of tolerance and risk is higher in those who suffer from EB because of its impact and that time of the essence. Dr. Baker said many proposed trials have petitioned the FDA to include some children in the studies. Dr. Drolet said it is important to add the need for a strict database/registry with phenotyping and genetic testing so that when the trials start there can be rapid enrollment and petitioning to the FDA for involvement of children. Dr. Silver said it will be difficult to get the entire registry done first, so it would help to have a parallel process.

Dr. Siegfried noted there is nothing said in the recommendations about devices, so the various devices are something for the subcommittee to consider adding.

Dr. Wilkin said part of getting younger children into trials earlier is having inclusion and exclusion criteria that describe populations at risk of mortality or a severely debilitating

permanent outcome. With that type of criteria, the FDA is being asked to look at the risk/benefit calculation rather than just being asked to get younger children in earlier. The trials are also an opportunity for prevention of severe morbidity. If what a pharmaceutical company is measuring is not one of these debilitating outcomes, their endpoints need to include these life-threatening and severely debilitating outcomes. Dr. Baker mentioned that the endpoints need to go far beyond the molecular correction of the disease; the FDA wants to know about patient-relevant outcomes such as improving range of motion, extension of life, reduction of infection, and use of pain medications.

It was noted that the committee's final recommendation sounds as if the fastest trials should be the ones supported. However, the longer a product is studied, the more unpleasant things are learned, so this recommendation needs to be nuanced. A lot of thought needs to go into the criteria for the choice of which trial to support.

Dr. Tom will take these recommendations back to the committee and update the document.

Infantile Hemangioma Subcommittee

Dr. Drolet said this subcommittee focused on clinical trials that could utilize the Pediatric Trials Network and found two opportunities. First is oral propranolol, assuming it receives FDA approval, as efficacy and safety data are available. The goal is to extend labeling to include this drug for high-risk patients such as preterm infants. Second is topical timolol, as people continue to use this drug off label and publish case studies, so its use will be widely adopted in the coming years. One preparation of the drug is currently approved for glaucoma in infants, so safety data are available for its application in the eye. This drug may be able to be extended to a new indication for a topical application. The research would probably involve some pharmacokinetic (PK) studies to determine peak time of systemic absorption and heart rate evaluations to determine biologic response, and then extend to safety and efficacy studies. For this kind of research, tools are needed that can capture the adverse events being seen in children who are using the drug off label. The drug seems safe, but some effects may show up later, so safety data need to be tracked.

Dr. Siegfried asked if the committee has some global recommendations that could be added to the document. Dr. Drolet said she would add some summary points.

Dr. Wade asked about instances where an FDA indication has changed for an ophthalmic solution for topical application. An instance noticed was when Allergan changed the application for Lumigan so it could be put on the eyelids rather than directly in the eye (this formula became Latisse). It was noted that for oral propranolol, the committee recommends working with the manufacturer to extend the labeling. For timolol, there is a U.S. pending patent on all beta blockers, so the manufacturers can never market for use of hemangiomas. Thus, the manufacturer does not have much incentive to put money into researching it. It was agreed that this possible limitation should be mentioned in the recommendations. It was mentioned that 80 percent of the drug is absorbed when put in the eye, but it is not yet known how much will be

absorbed through topical skin application. There is potential for overuse and systemic exposure, so PK studies should be conducted.

Drug Development Issues Subcommittee

Dr. Siegfried said this area includes threads of important points from all the subcommittees. The group summarized the committee's thoughts about uncommon, but not life-threatening, conditions. They noted the following issues:

- Product labeling that overemphasizes the theoretical risks of new treatments compared to well-established risks of poorly controlled disease
- An underappreciated risk for adverse events from the widespread off-label use of drugs for skin diseases that lack evidence-based treatments
- A lack of well-defined acceptable risk parameters and clinical trial guidelines for development of new drugs in children with nonlethal, life-altering skin diseases.

The goals are:

- To state the need for well-defined regulatory clinical development pathways to inform, facilitate and incentivize new treatments for these pediatric dermatological diseases
- To generate an official request from the BPCA/*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to the FDA to seek input from experts outside the agency
- To offer initial suggestions for inclusion into a level 1 guidance document.

Dr. Siegfried said the subcommittee considers this document to be general opinion that can help get things moving. The rest of this recommendation document provides background about why this topic is important, specific areas of unmet needs and the lack of FDA-approved medications to treat many skin diseases, specific parameters that are important, age limits, objective endpoints that are important to have, efforts such as the Pediatric Dermatology Research Alliance (PDRA), protocol designs, and parameters such as incorporating parental opinion into study designs to encourage enrollment and retention.

Dr. Hebert asked if this document should include the quandary of pediatric dermatologists who are trying to move forward but with limited knowledge about the best methodologies to use for certain disease states, which is why they are looking to the FDA for specific guidance. She said she hopes for FDA feedback.

Dr. Taylor-Zapata noted that these recommendations are going directly to the NICHD/BPCA, but that many issues within pediatric trials go across specialties. The BPCA has talked about providing feedback to working groups and allowing them to hear from FDA specialists who work in their areas. The BPCA is creating a formal feedback mechanism that will begin in spring 2013 and will arrange for conference calls between FDA representatives and the working groups.

A participant mentioned that a preliminary draft could be put together for the FDA, or the FDA could be asked to put this topic at the top of the list for guidance documents that the agency

develops for the next year. It was noted that the Federal Advisory Committee Act states that if the FDA is working with more than one person/group at a time, it has to be a public/transparent process, so it is difficult for the FDA to sit with a particular group to create a guidance document. In addition, pharmaceutical companies are reluctant to develop new topical products because they do not want to go into a risk-averse FDA setting that regulates, monitors, and advises about drug development. A guidance document could make this process seem more feasible and encourage companies to address unmet needs.

Dr. Wade said this is an important point and that it is difficult to know how to get the FDA to be responsive. The needs in the labeling arena are unique, and what has helped in other pediatric labeling venues is extending older child/adult indications down into the neonatal range.

Dr. Tom asked if the FDA would fund a workshop about this topic. Dr. Siegfried said she could make this a committee recommendation. Having a working group around this topic would require participants who know the clinical issues for common conditions and experts who know what guidance documents should include. Dr. Drolet said it may help to focus on specific challenges of treating dermatology conditions. Dr. Hebert suggested looking at when propranolol was introduced in adults and then brought into the pediatric population for cardiac disease; this may serve as an initial basis for understanding how drugs can be transitioned to the pediatric realm, particularly from non-dermatologic use to dermatologic use.

Dr. Siegfried will summarize the next steps, provide a summary of committee recommendations, and list the overall goal as being to learn more about guidance documents.

Severe Atopic Dermatitis Subcommittee

Dr. Eichenfield said this group is working on two templates: one for systemic therapy for severe atopic dermatitis and one for use of topical calcineurin inhibitors (TCIs) in children down to 3 months of age. Although his group has not completed its recommendations document, he gave an overview of what will be included.

There are only five topical agents that are currently FDA-approved to treat severe atopic dermatitis. The TCIs are approved for children ages 2 and older for non-continuous use. They have a broad set of efficacy data. This subcommittee is posing the question of whether the black box warning for TCIs should be reconsidered. He noted that the desired outcome is evidence that TCIs do not lead to cancer and are safe for children ages 3 months and older with severe atopic dermatitis. They may, in fact, be well suited to long-term management. He said that the FDA black box warning risks have not been proven, and that although the warning may not be removed, the subcommittee wants FDA input and perhaps a change in labeling.

It was recommended that this subcommittee look at the transcripts of the FDA meeting where there was discussion about the black box warning and Novartis' direct consumer marketing. The FDA committee's recommendation was solicited not just due to evidence of concern, but because of marketing. The concern was that the drug promotion was causing widespread use in

young children in cases where there is uncertainty after long-term effects. The transcript says, “If a black box warning is the only way to stop the DTC marketing, it will be done. My measure of success is the reduction of sales by 50 percent.” Dr. Siegfried said that although marketing played a role, increased sales also spoke to an unmet need for treatments that are not corticosteroids. People want steroid-free treatments so they often turn to ineffective and untested homeopathic treatments that do not have efficacy data.

More data are need about the health of nontreated children with severe atopic dermatitis and the development of the immune system in children who are treated. Dr. Eichenfield said there are emerging data about comorbidities, and it was agreed that those should be included in this document as a rationale that undertreatment may have far-reaching effects (for example, attention deficit hyperactivity disorder, lack of sleep, and gastrointestinal issues). Dr. Siegfried asked whether there are enough data to ask for a change in labeling, and it was explained that this would need to be researched and evaluated, which would be a lot of work. It was determined that it would be more efficient to simply explain this unmet need to the FDA.

Dr. Eichenfield explained that the section about severe atopic dermatitis is not yet complete, but he gave highlights of the section, including the following points. The subcommittee recommends supporting the consideration of pediatric patients early on in trials for new treatments and supporting comparative effectiveness studies for immunosuppressive and cytostatic agents that are utilized without labeling for this condition. There are no FDA-approved agents for this condition. The needs assessment will propose treatment for children 3 months of age and older. The adverse effects section is a broad list and is not yet completed, but there is a need to assess disease modifying effects and potential long-term side effects. The document will also include discussion of the current standard of care, secondary effects, ethical concerns such as carcinogenic risks, currently available agents for treatment, ongoing clinical trials, needed studies, present outcome measures such as quality of life, and medicines in development that do not include children in the trials. Final recommendations will include comparative studies and inclusion of young patients with severe atopic dermatitis in trials.

Dr. Siegfried noted that excluding children is an ethical concern, because it is a missed opportunity for controlling the disease. She asked if this area be funded separately by PDRA or under “outcome measures.” A participant noted it would be useful to look at clinical standards of use for these medications to gather preliminary data and look for funding for pilot studies. Dr. Baker said as long as there is a research focus to a study, it is possible to apply for funding.

Participants discussed the need for further studies and the current PDRA trial. It was mentioned that it would be helpful to survey the patients as they are being treated, but that it is difficult given time constraints and lack of funding. It was suggested that the work done thus far should be called a “preliminary study” so the FDA will be more likely to want to get involved and help with funding for an official study.

Action Items:

- Dr. Tom will take the genodermatosis recommendations back to the subcommittee and update the document.
- Dr. Siegfried will summarize the next steps for the Pediatric Drug Development Issues document, provide a summary of subcommittee recommendations, and list the overall goal as being to learn more about guidance documents.
- Dr. Eichenfield will complete the severe atopic dermatitis document for submission to the group.
- Revisions should be submitted to Dr. Siegfried by November 12, 2012.