

**Best Pharmaceuticals for Children Act (BPCA)
Cough and Cold Therapeutic Working Group Conference Call
July 24, 2009
1:00 p.m.–1:30 p.m. ET**

Participants

Danny Benjamin, M.D., Ph.D., M.P.H., Duke University Clinical Research Institute
Ian Paul, M.D., Pennsylvania State University College of Medicine
William Rodriguez, M.D., Ph.D., Office of Pediatric Therapeutics, U.S. Food and Drug Administration (FDA)
Heinz Schneider, M.D., Consumer Healthcare Products Association
Brian Smith, M.D., M.H.S., Duke University Clinical Research Institute
Wayne Snodgrass, M.D., Ph.D., University of Texas Medical Branch
Amy Taylor, M.D., M.H.S., Center for Drug Evaluation and Research, FDA
Perdita Taylor-Zapata, M.D., National Institute of Child Health and Human Development, National Institutes of Health (NIH)
Ronald Turner, M.D., University of Virginia School of Medicine
John Van Den Anker, M.D., Ph.D., Children's National Medical Center
Teri Moser Woo, R.N., Ph.D., CPNP, University of Portland

Purpose

The purpose of the meeting was to review group members' evaluation of priority areas of research needs and to agree on the top four priorities.

Introduction

Dr. Taylor-Zapata summarized the working group's activities to date. Two previous conference calls were held in March and May, and in June a list of recommendations for research priorities derived from those two calls was sent to group members to evaluate. The group agreed to have this third call to discuss the results of the evaluation and agree on priorities. There were two evaluations: the first was based on a list of general ideas pulled together from the two calls, and the second used an evaluation form prepared by Dr. Paul that reorganized the recommendations and asked the respondent to rank each item as priority 1, 2, or 3. Everyone responded to that evaluation form. Dr. Taylor-Zapata said the slides presented during the call would be e-mailed to everyone.

Presentation of Evaluation Results

Dr. Paul said he suggested that a second survey would be helpful because the wording of some of the priority areas in the first survey made it difficult to get accurate results. He worked with Dr. Taylor-Zapata to synthesize the results from the two surveys to try to identify the group's top research priorities. Dr. Paul noted that four people responded to both surveys, so he removed the votes from those people who answered the second survey from the responses to the first survey

to avoid having their votes counted twice. Additional topics for the second survey were included because some things were missing from the first survey, and other things were lumped together that were not identical issues. The second survey included a few more options.

Dr. Paul presented a slide with the results from the first survey and cautioned the group that the numbers in red were a bit deceptive because of overlapping topics. The highest ranked topic on both surveys was to define better clinical endpoints for both objective and subjective studies. The group was also interested in pharmacokinetics (PK) in children younger than age 2. The first survey included rankings by 7 group members, and the second survey included rankings by 11 members. The second page of the slide included several comments by group members.

Another slide summarized results from the second survey. Again, Dr. Paul cautioned the group about the numbers in red. He explained that when he tried to synthesize the surveys with Dr. Taylor-Zapata, he reorganized the topics and lumped some things together differently. The majority of the group listed the development of clinically meaningful endpoints as the top priority. The next three topics listed on the slide all had to do with efficacy. Group members emphasized several different age groups that need to be studied. Seven of 11 members who answered the survey said some type of efficacy studies should be one of the top three priorities. Dr. Paul said that the priority rankings based on the surveys were up for discussion.

The formula used to calculate the numerical rankings was explained at the bottom of the slide. A few comments from group members were on the second page.

Dr. Paul said the first topic listed regarding endpoints was clearly the number one priority for the group and was ranked number one in both surveys. The other three priorities, when re-lumped back together, were each given about the same priority rank.

The survey results produced the following four priority areas:

1. Develop clinically meaningful endpoints and validated tools to measure them (subjective and objective)
2. Perform efficacy studies of orally administered over-the-counter cough and cold ingredients (Dr. Paul merged the three different age categories based on the varied responses from the group)
3. Perform PK studies of orally administered cough and cold ingredients in children including the study of pharmacogenetic variability
4. Perform studies to better elucidate the primary biochemical mediators of cough and cold symptoms to identify new targets for drug therapy.

Discussion

Dr. Rodriguez commented that it was interesting that the top two priority areas came up at the FDA Advisory Committee as areas that would benefit from further development.

Dr. Van Den Anker inquired about the order of the priorities, noting that PK studies should be done before efficacy studies. Dr. Paul replied that the priority order was based on the results of the voting and is not the order in which studies should be performed.

Dr. Paul asked Dr. Taylor-Zapata whether the priorities were what the group wanted to present at the November meeting. Dr. Taylor-Zapata said the priorities to be presented at the annual meeting could be the outcome of the call, or the group could finalize them by e-mail.

Dr. Benjamin asked whether the BPCA mechanism is consistent with finding new targets for therapeutics. He thought that although finding new targets is an admirable goal, endpoints and PK safety and efficacy would be more consistent with the BPCA. Dr. Taylor-Zapata responded that the group's recommendations are to the FDA as well as the NIH. BPCA calls for a relationship between the two agencies. In the new BPCA, the NIH can broaden the mechanisms for doing studies. Other types of funding mechanisms such as grants are possibilities. The group's recommendations were not limited but left open to whatever the group felt was important.

Dr. Turner noted that the recommendations were focused on children, and he wondered whether it is appropriate for mechanistic studies in children to be a priority when those studies have not been done systematically in adults.

Dr. Benjamin agreed with Dr. Turner and said many products are used every day for which safety and efficacy are not known. New therapeutic targets are nice, but this year, 2 million children younger than age 2 will get cough and cold medications. He thinks that the focus should be safety and efficacy. There is a need to find out what children are being exposed to.

Dr. Woo agreed. Parents are making decisions about the use of medications based on ads and are not asking their primary care providers for advice.

Dr. Snodgrass said he was comfortable focusing on endpoints and efficacy. The idea of establishing endpoints would be a good priority that applies to adults as well as children. PK can be part of efficacy, but he would want to determine the endpoint(s) and some degree of efficacy first before going on to get additional PK data. Regarding biochemical mediators, the initial focus should be in adults, but down the road, the research should address the developmental aspects and the expression and response to viruses in different age groups.

Dr. Benjamin said that one of the reasons pediatric studies have failed through the exclusivity program is that people designing the trials did not get PK right and did not do dose-ranging studies; they went early into efficacy studies. He asked whether Dr. Snodgrass was saying to get just enough PK data to design the efficacy studies well or that efficacy trials could begin right away.

Dr. Snodgrass said he was suggesting the former as well as initial dose-ranging studies. Dose-ranging studies have never been done for older products in the current monograph, so if initial

dose ranging is done, it would incorporate some safety aspects. If efficacy can be determined, it would give the basis for more extensive PK studies.

Dr. Rodriguez said he assumed Dr. Snodgrass was talking about these studies on the background of having decided what meaningful endpoints are and having validated tools to measure them. Dr. Snodgrass said that was correct. The pharmacodynamics (PD) area is very important. The reason he kept bringing up biochemical mediators and other targets is because it is sort of a two-stage approach, beginning with studies as they discussed during the next 3–5 years, followed by longer range work that would address other mediators and targets. Newer drugs may become available down the road that are more selective and would be more effective.

Dr. Paul commented that Robert Nelson, M.D., Ph.D., said he did not want to duplicate industry efforts. Industry is doing a lot of PK, although not in children younger than 2. Dr. Paul wondered whether, if industry comes out with a large number of PK studies, the group would still want PK studies to remain a priority. Dr. Benjamin responded that two sets of data from the NIH and industry could be complementary.

Dr. Paul said there seemed to be pretty good agreement about the topic areas covered. He asked that group members feel free to send any wordsmithing suggestions or suggestions for the top three priorities. He was not sure whether the fourth priority area should even be mentioned at this point. Dr. Rodriguez suggested including it as something that should be a focus in the future. Dr. Woo agreed that it should be included as a long-term goal.

Dr. Benjamin suggested including a timeline to give people a sense of when and how these things might be accomplished, such as:

- During the next 12–24 months, look at endpoints
- During the next 18–36 months, design and start initial PK/PD studies
- During the next 24–48 months, achieve final resolution of PK/PD as they relate to efficacy.

Dr. Snodgrass agreed with the idea of including a timeline, although it might vary. Dr. Paul said such a timeline could easily be included in the presentation at the meeting.

Dr. Taylor-Zapata and others expressed appreciation to Dr. Paul for taking the lead regarding the priority areas.

Next Steps

- Working group members will contact Drs. Paul and Taylor-Zapata with wordsmithing suggestions or other comments.
- Circle will prepare and distribute a draft of the meeting minutes.
- The top four recommendations will be submitted for discussion at the annual BPCA scientific prioritization meeting, November 18–19, 2009.