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## AMERICAN COLLEGE OF CLINICAL PHARMACOLOGY

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April 28, 2005

Sandy Long, CMP  
Circle Solutions, Inc.  
8280 Greensboro Drive, Suite 300  
McLean, VA 22102

RE: Public Comment on the 2005 BPCA Off-Patent Drug List

Dear Ms. Long:

I am writing this letter on behalf of the American College of Clinical Pharmacology (ACCP) in response to Drs. Mattison and Lasky's February 16, 2005 letter requesting comment on prioritization for drugs included in the comprehensive, 2005 Best Pharmaceuticals for Children Act (BPCA) listing. The ACCP is an international professional organization whose membership includes highly trained individuals whose research, clinical practice and/or academic endeavors focus specifically in the area of clinical pharmacology. Thus, considering the nature of Drs. Mattison and Lasky's request, we feel particularly competent to provide our opinions regarding important medications that should be focused on during this year's scientific meeting to be held in November 2005.

First, the College would like to applaud the efforts of the Institute and the important Inter-Institute partnerships with the FDA and our elected officials for continuing the unwavering support of both the spirit and intent of the BPCA initiative as well as the BPCA's predecessor initiatives and legislation. Most of the more recent advances that have been realized in pediatric pharmacotherapeutics have occurred as a direct result of the strong support and leadership the Institutes and its partners have shown over this rather lengthy process. The College unconditionally supports these efforts and if the need would ever arise that the expertise of our membership would be of value to any of these initiatives, our members would enthusiastically make themselves available for such consultation and input and promptly respond to any invitation extended.

To introduce myself, I am a Professor of Pediatrics in the Department of Pediatrics at Case Western Reserve University and am the Director of Pediatric Clinical Pharmacology and Toxicology at Rainbow Babies and Children's Hospital in Cleveland Ohio, the primary pediatric teaching and practice site for the Department's full-time faculty. I also have the pleasure of serving the ACCP as councilor to the President and as a non-voting member of the College's Executive Committee. The College recognizes its important responsibility to community health initiatives, whether in the US or abroad, and has established just such a process for its expert members to provide evidence-based authoritative scientific opinion whenever invited. I have the honor of serving as the chair of a working group of College members expert in pediatric pharmacotherapeutics and we offer our suggestions below. Per the instructions and requests outlined in the February 16 letter, we have focused our opinions on the off patent drugs listed in Table 1 and we comment on those non-oncologic drugs that our working group believes should receive the highest of priority. The comments I have outlined below represent my summation of the College's working group's deliberations.

Priority Non-Oncologic Drugs from the 2005 BPCA List of Off-Patent Drugs

Antimicrobial Drugs

Anthelmintics:

1. albendazole: no liquid or chewable formulation is available. Literature-based dosing guidelines of questionable validity exist with most addressing dose by body weight, i.e., < 60 Kg or > 60 Kg body weight or as an absolute 200mg or 400 mg dose. Thus, dosing requires critical evaluation as well as patient safety and tolerability. Although very little of the drug is absorbed systemically with oral administration in adults, the drug is a known CYP 450 substrate (CYP3A4) and CYP 1A2 inducer. Possible age differences in absorption should be assessed.
2. mebendazole: is available as a chewable tablet though a liquid might also be desirable. The information outlined for albendazole above is also pertinent for mebendazole with the exception of CYP isoform induction. It appears that mebendazole is a substrate for but may not induce specific CYP isoforms. Nevertheless, if the drug is as poorly absorbed into systemic circulation as in adults these possible CYP interactions may be simply of academic interest.
3. thiabendazole: available in both a chewable and suspension formulation. Requires pharmacokinetic data in children.

Antifungals and Antibacterials:

1. amphotericin B (Lipid) Complex: the lipid-based formulations of amphotericin B are now the preferred formulations due to their patient tolerability and more recently, adaptability to higher dose therapy. Although specific pediatric dosing data are limited it would appear that the study of doses higher than 5mg/Kg body weight / day may be warranted as well as any data regarding these drugs' utility for the treatment of fungal meningitis. Also, combination antifungal drug therapy is evolving as a preferred treatment strategy in these critically ill patients.
2. cefipime: an important broad-spectrum antibiotic used with increasing regularity in the treatment of hospitalized pediatric patients of all ages. A large body of published experience exists across a broad age range for this drug, which would support more critical labeling for use in pediatrics.
3. ceftizoxime: although its popularity in pediatric practice is decreasing, somewhat a result of its deficient label, it does offer an effective broad-spectrum antibacterial agent that is most likely very cost effective. It would appear that sufficient published experience exists across a broad age range to permit more specific labeling.
4. fluconazole: requires proper dose and safety studies when used as a component of combination antifungal therapy, i.e., when combined with a polyene or echinocandin antifungal drug. Improving published experience exists for its use for esophageal candidiasis.
5. flucytosine: adequate published data (both PK and tolerability) would appear to be available to permit the derivation of appropriate dose guidelines.
6. metronidazole: requires limited research strategy targeted towards supplementing currently available published data on age-appropriate PK to permit integrated PK-PD modeling to enhance the value of the present label.
7. mupirocin: it would appear that sufficient published data exists to enhance the current label particularly related to broader, topical uses for line infection prophylaxis.
8. nafcillin: for over 35 years one of the most commonly used parenteral anti-staphylococcal penicillins used in pediatrics that would appear to require only minimal PK studies to complement published experience.
9. trimethoprim: appears sufficient published experience exists that would permit revising the current label.

Cardiovascular Medications

1. chlorothiazide: frequently used in combination with furosemide and spironolactone in premature, full-term, young infants and children and often in the intensive care units. In the intensive care units the drug is often administered by intravenous administration and then “switched” to oral dosing when the patient is more stable. Such use / combination use and proper conversion dosing requires limited PK data (e.g., drug bioavailability vs age) such that this contemporary practice information is incorporated in the label.
2. digoxin: one of the most commonly used cardiac active drugs in pediatric practice. With current analytical sensitivity and specificity which excludes the influence of digoxin immunoreactive substances, age appropriate integrated PK-PD data could be obtained and combined with published experience to markedly enhance the value of the drug’s label.
3. enalaprilat: requires age appropriate integrated PK-PD and patient safety data particularly for use in the treatment of heart failure.
4. fenoldopam: this agent appears to have great potential in patients with cardiovascular disease. The critical study of age appropriate integrated PK-PD data are necessary. It would appear that the type of data required for inclusion in a meaningful label would require a major initiative, particularly considering that the vast majority of children who would benefit from the drug are critically ill.
5. hydralazine: it would appear that sufficient published experience exists that would permit a more meaningful revised label.

Sulfonylurea Medications

The unfortunate increase in the incidence of childhood and adolescent obesity and co morbid “Type II” diabetes underscores the importance of the comprehensive study of this class of compounds for the treatment of older children and adolescents.

Drugs with Sufficient Published and Clinical Experience

Recognizing the enormity and complexity of any initiative to enhance the value of the drug label to contemporary pediatric practice, the ACCP working group felt that in addition to “priority” that another level of priority exists for targeted drugs i.e., that of drugs with sufficient published experience. Once a comprehensive, critical evaluation and summation of all available published data is completed for a select group of drugs an alternate strategy could include the convening of independent “expert committees” for each agent whose charge is to evaluate the published experience and determine if sufficient data exists to revise the label. It would seem that such an approach would enhance the pediatric value of the label within a cost efficient framework. The opinions of these working groups could be made available for public comment, revised if necessary and then included in a special “Pediatric Consensus Panel Guideline” section of the label. In addition, such an evaluation may better define necessary, focused research endeavors required to provide needed data for specific agents. Moreover, such targeted research endeavors may enhance the depth and breath of the data for important pediatric drugs in a very cost rational manner.

The following represents the working group’s initial selection of non oncologic drugs from “Table 1 Off-Patent List” that would appear to meet the criteria of sufficient published experience for review by an expert advisory panel. Please note that some of the drugs noted here have also been commented upon above.

6-mercaptopurine, amoxicillin / clavulanate, cefdinir, cefepime, ceftizoxime, cefuroxime, cefprozal, cephalexin, clonazepam, dexamethasone, dimercaprol, epinephrine, fludrocortisone, insulin-regular, magnesium sulfate, metaproterinol, methylprednisolone, phenobarbital, phenytoin, pralidoxime, prednisone, prednisolone, pyridoxime, silver sulfadiazine, sulasalazine, terbutaline, theophylline, ticarcillin / clavulanate and trimethoprim.

In addition to the above, the working group felt that the tremendous resurgence in head lice infestations (*Pediculus capitis*) throughout the world and the proliferation of “unstudied complimentary therapies” underscores the importance of the need for continued research in this area. Below I have summarized the recommendations of the College’s working group regarding this important pediatric infectious disease.

#### Epidemiology and Current Pediatric Practice: Pediculosis Capitis

The prevalence of head lice is estimated to be from 1 to 3% of the population in industrialized countries. Infestations affect all socioeconomic groups and are common among children aged 3 to 12 years, particularly in girls. Blacks are affected less than are other races. Malathion, an off-patent drug not listed for study by the BPCA Annual List Prioritization Working Group, Feb 2005, is FDA-approved for the treatment of head lice and their ova of the scalp hair in children 6 years and older. Due to safety concerns, malathion is not a first line treatment for scabies or lice, but “safer” alternative medications, including permethrin, are not always effective at eliminating scabies or lice. Common alternatives to malathion for the treatment of scabies in children are permethrin cream 5% (Acticin™, Elimite™), which is available by prescription, and the nonprescription product Nix™ which contains permethrin 1% as a hair cream rinse. The alternatives to malathion lotion for treatment of head and pubic lice in infants or children are two nonprescription products: Nix™ which is permethrin\* 1% lotion/cream rinse, and Rid™ which is pyrethrum extract 0.33% with piperonyl butoxide 4% in a shampoo formulation. Nevertheless, drug resistance continues to pose an important clinical challenge and appears to be more of a problem with these products than with malathion. Clinical cases of drug resistance have been reported with pyrethroid products and lindane. Moreover, limited recommendations exist for the use of any of these products in the younger child < 6 to 8 months of age. Malathion (Ovide™) lotion 0.5% is applied topically to the scalp and hair. The medication is left on for 8 to 12 hours prior to rinsing and a thorough washing. While malathion is highly effective when used as directed, repeat application is sometimes necessary, which raises concern for cumulative toxicity.

#### Clinical Challenge and Gaps in Current Knowledge of Pediculosis Treatment

As an organophosphate insecticide, malathion acts as a neurotoxin to insects but does not spare the human nervous system. Used therapeutically as a pediculicide, malathion can cause moderate skin irritation, drowsiness, muscle twitching, and rarely seizures. There have been additional adverse health effects related to cholinesterase inhibition in human workers exposed to malathion. As a pesticide, malathion is classified in the U.S. Environmental Protection Agency’s (EPA) acute toxicity category III (where I is the most toxic and IV is the least toxic). More information is needed about the optimal use of malathion as a pediculicide in children, including the best application procedure, duration of contact with skin and hair, and the advisability of repeat applications, particularly the time interval between applications. Further, more information is necessary about patient and formulation factors that increase absorption and toxicity of malathion and its conversion to malaoxone, a highly potent metabolite. Additionally, information is needed on malathion’s long-term neurological effects in the developing central nervous systems of children. This added knowledge would aid in the design of new formulations and age-adjusted dosage regimens that minimize toxicity.

Considering the brief background provided above, the working group determined that the increasing resistance to pyrethroid pediculicides and the relative lack of new chemical entities to treat human lice infestations, that the safe use of malathion in children requires further research, particularly in the following two areas:

1. Evaluate existing data (experimental animal data as well as human exposure data) from the EPA and the CDC for insight into the long-term neurological effects in developing central nervous systems of children.
2. Study the percutaneous absorption of malathion from the marketed lotion formulation. This could be accomplished by analysis of urinary metabolites in children receiving topical malathion as well as determination of RBC cholinesterase activity.

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In conclusion, the ACCP fully endorses the intent and spirit of the BPCA initiatives and is in complete support of the Institute's and Agency's important efforts in these important partnered efforts.

On behalf of the College's working group we sincerely hope that the above comments will be of value to you and your colleagues as you formulate your next prioritized list of "off patent drugs" for focused study. If you or any of your colleagues believe that the ACCP may be of any further assistance with these important endeavors or any others in the future, please do not hesitate to call upon the College.

Sincerely,

A handwritten signature in cursive script that reads "Michael D. Reed".

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