Reviewer 1

Comments about pharmacokinetic analysis of fixed-dose combinations for pediatric tuberculosis.

This submission presents a detailed pharmacokinetic analysis of three drugs for treatment of Tb based apparently on drug concentration vs time endpoints in an internal WHO document (ref to Donald PR, 2008). The authors then use this analysis to recommend a fixed dose product containing INH 150 mg, Rifampin 200 mg, and Pyrazinamide 400 mg. The dosage is calculated as a fraction of tablet to multiple tablets based on weight. The doses are approximately INH: 15 mg/kg, rifampin: 20 mg/kg, and pyrazinamide: 40 mg/kg. Presumably this is once a day dosing. An addendum suggested that a rifampin amount of 250 mg/tablet rather than 200 be considered.

The kinetic analysis suggests that these doses will lead to therapeutic efficacy. The analysis does not address the issue of toxicity. There are several points to consider. The first is the end point used, fraction of the day at which the drug concentration is above a threshold value. Antimicrobials can be classified into two pharmacodynamic classes: time-dependent killing or concentration-dependent killing. Some antimicrobials like the beta lactams and macrolides increase their fractional kill as a function of time above a threshold concentration value. Others such as aminoglycosides and fluoroquinolones increase their fractional kill by increasing the peak concentration irrespective of the time above a threshold concentration. Please see the fine review by Craig WA. Pharmacokinetic/Pharmacodynamic parameters: rationale for Antibacterial Dosing of Mice and Men. Clinical Infectious Diseases 1998; 26:1-12.) I was not able to find data to determine the pk/pd characteristics of the usual Tb drugs. However, both the aminoglycosides and fluoroquinolones are concentration-dependent killing drugs in pyogenic infections. Perhaps, their Pk/Pd relationships are related to their mechanisms of action and are the same for Tb. The fact that effective therapy of Tb occurs with three times a week dosing at higher than daily doses suggests very strongly that these drugs have concentration-dependent effects rather than time-dependent effects. The experience with aminoglycosides that once a day dosing gives equal efficacy with less toxicity that three times a day dosing gives me concern that the recommended doses of pyrazinamide lead to excessive exposure in those children receiving more than 30 mg/kg. Goodman and Gilman, 11th ed, 2006, p. 1211 states that liver disease occurs in about 15% of people taking 40-50mg/day and regimens of up to 30 mg/day are safer. This issue of safety vs efficacy for pyrazinamide should be addressed by pediatric Tb experts.

A second major issue is the wisdom of recommending a three drug tablet/regimen when the WHO treatment guidelines and the current recommended care world wide is for an initial four drug regimen. The usual one, and the one recommended by WHO, is to add ethambutol to the three drugs in the recommended tablet. When the pediatric cases of Tb are in communities with a reasonable risk of drug resistant infection, it would be poor practice to use only three drugs as initial therapy. Certainly, consideration of a four drug combination pediatric tablet must be included in any consideration of pediatric fixed-dose combination tablets. The alternative of frequent injections of streptomycin appears as a less desirable choice to this reviewer for these patients. The current Model List does include this 4 drug fixed-dose combination tablet at adult strength.

Another major issue is the addition of pyridoxine to all isoniazid-containing tablets. According to Goodman and Gilman (p. 1207) 2% of patients receiving isoniazid at a dose of 5 mg/Kg without pyridoxine get peripheral neuropathy. This incidence goes up to 10 – 20 % at higher doses. This neuropathy can be prevented by giving pyridoxine concurrently with the
INH. Pyridoxine supplementation prevents the other neurotoxicity from INH as well. The doses received by children taking the suggested tablet would be in the 10-15 mg/Kg range, well above the 5 mg/Kg range of 2% neuropathy. An objection to adding pyridoxine might be that adding it would raise the cost and complexity of the formulation. This would have to be balanced by the benefits of a reduction of toxicity. Perhaps a formal cost/benefit analysis would be helpful in addressing this issue. If there are technical reasons why pyridoxine cannot be added to a fixed-dose Tb drug formulation containing isoniazid, then the Expert Committee should add a pediatric dosage form of pyridoxine to the Model List with the report stating that it is to be given with any INH-containing regimen to prevent neurotoxicity. (The age restriction on the official approval of ethambutol is for children over 13 since patients under that age may not be able to report visual toxicity symptoms. Certainly children under that age may be even less likely to report neurotoxicity symptoms. While I know of no way to reduce the risk of ethambutol toxicity and it is still appropriately recommended for children younger than 13, accepting this risk, one can reduce or abolish the risk of INH neurotoxicity with pyridoxine supplementation.)

The last major issue relates to the pharmacokinetics of these drugs in the first month or two of life. Maturation of the drug metabolism pathways develop over time. There is nothing in the report that addresses this topic. There is also nothing that addresses infants less than 5 Kg. These two points should not be ignored.

A major policy issue for the selection and use of essential medicines is what advice to give when the data is insufficient to give a strong evidence-based recommendation. This relates to the appropriate dose of pyrazinamide for children, not offering a tablet containing ethambutol for children less than 13 years, and not stating anything about treating Tb in children less than 5 kg. This lack of advice or recommendations when the evidence is insufficient has been troubling the United States Preventive Services Task Force. After all, if the “best” minds with the time to consider all the evidence are unable or unwilling to suggest to the practitioner what to do, how is the busy practitioner supposed to determine how to manage the next patient with the condition? The Preventive Services Task Force has addressed this issue and has developed a way to advise practitioners without violating the tenants of evidence-based medicine (Petitti DB, et al. update on methods of the U.S. Preventive Services Task Force: Insufficient Evidence. Ann Intern Med 2009; 150: 199-205). As the WHO continues to revise and develop evidence-based treatment guidelines, it should consider the advice it gives when the evidence is insufficient for a strong recommendation. With respect to this Expert Committee, when a fixed-dose pediatric Tb drug formulation is added to the Model List, the report should discuss how it should be used, or if it should not be used, what should be used to treat the very young and those children less that 5 Kg of body weight who have tuberculosis.