Reviewer's report

Title: Covariates of intravenous paracetamol pharmacokinetics in adults

Version: 1
Date: 15 July 2014

Reviewer: Sam Salman

Reviewer's report:

Minor Essential Revisions

Materials and methods.
1. A table with key descriptive information of the 7 different studies would assist the reader in evaluating the degree of heterogeneity. i.e. age (median, range), weight (median, range), FFM (median, range), sex, duration of sampling, assay method.

2. Page 7 – typo: RUV is defined as both residual unexplained variability and residual unidentified variability.

3. Page 8 – please explain in the text why a 2 compartment model was assumed not evaluated against other models (1 or 3 compartments)

4. Was a step-wise procedure used for the addition of covariates or were they tested in stages (ie. size descriptors first)

5. Page 10 – was the bootstrap stratified according to study or any covariate?

Results
6. There is no text regarding model evaluation (see note below regarding table 1)

Discussion
7. All healthy subjects were aged below 37 years old. As age is a significant covariate in the model this potential bias should be discussed.

8. Page 13, paragraph 3 – change in fat per kilogram body weight is used to explain the change in V noted with age. Given the presented model tries to account for such changes with the use of NFM are the authors indicating that this size descriptor is not able to explain the increased fat percentage noted with age, and therefore, is there another size descriptor which would perform better and be able to account for these changes?

9. Page 14, paragraph 1 – the greater increase in CL in pregnancy (1.58 vs 1.23) noted in reference 45 may in part be caused by the fact that a size descriptor was not utilised and the pregnant women were larger. The conclusion of reference 46 states “… the absorption and disposition of acetaminophen, when used in a standard oral dose, are not affected by pregnancy.” and therefore need further explanation in the discussion. It is current location the reference is misrepresented.

10. Page 14, final line – typo, 11.6 mg/L appears twice in one line
Tables
11. A table comparing the studies would assist with evaluation of this pooled analysis. (see above)
12. With respect to the variance of RUV.
   a. All other variability parameters are presented as percentages, for consistency this should be changed.
   b. Did the authors investigate if a particular study had a higher (or lower) RUV using this variance term?
13. The 95% CI from the bootstrap includes zero for FfatCL. What is the reasoning to include this poorly estimated parameter in the final model? (assuming that a stratified bootstrap was performed)

Figures
14. Figure 1 - it is not possible to evaluate this plot after 36 hours as the degree of overlap of the shaded areas is not clear

Discretionary Revisions

Materials and methods.
1. Page 9 – please indicate in the text that a linear model is used for the effect of age on CL and V

Results
2. The change in OFV for the different size models is included however it would be useful to present the same information for other significant covariate relationships.

Discussion
3. Page 13, paragraph 1 – were the authors expecting a gender effect on clearance?
4. Page 13, paragraph 2 – the authors could include the estimates from paediatric data to illustrate the similarity with the present pooled analysis
5. Page 15, paragraph – the authors introduce the concept of unexplained vs explained parameter variability here. It may be worthwhile to include these terms in the methods section. It would be informative to know the extent of explained parameter variability, the values of BSV/BOV for CL and V without any covariates could be included for this comparison.

Figures
6. Figure 1: the y axis could be a semi-log plot could be used to better visualise the VPC

**Level of interest:** An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests