Comments on

CPMP Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function (CPMP/EWP/2339/02, Draft, 26 February 2004)

German Region of the International Biometric Society

General comments:

1. Reference on document 'Pharmacokinetic Studies in Man' (p. 1, enumeration at the top, 1st point)

The requirements with regard to the statistical analysis and presentation given in the document 'Pharmacokinetic Studies in Man' go far beyond of those given in section III.2 of the NfG draft under consideration. Is this really intended? If not, a reference on the general pharmacokinetic guidance document could be made in section III.2.

2. Study population (p. 4, section II.2, last paragraph)

'The number of subjects enrolled should be sufficient to detect clinically relevant pharmacokinetic differences. The "clinically relevant" difference should be pre-specified and justified …'

It should be made clear whether it is the aim of the studies under consideration to *show* a pharmacokinetic difference or to *exclude* a relevant difference. The only recommendation to enrol 'a sufficient number of subjects' is inappropriate for the latter aim. This so-called 'power approach' was discarded in bioequivalence many years ago and should not be resuscitated. It is necessary rather to incorporate the opposite of the actual aim of the study

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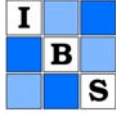
into the statistical (null-) hypothesis to be tested. The NfG on the investigation of bioavailability and bioequivalence and the NfG on the investigation of drug interactions should be considered with this respect (e.g. the definition of equivalence regions).

3. Dose reduction in hepatically impaired patients (p. 4, section II.3, last paragraph, last sentence)

In section II.2 (Study population), it is recommended to use a within control group. Furthermore, it is suggested to consider - in a first step - subjects with moderate impairment and healthy controls. For drugs showing a substantial first-pass effect due to extensive hepatic metabolism a dose adjustment (section II.3, Drug administration) in the hepatically impaired group(s) is proposed for safety reasons. Thus, the control group may receive a different dose in this situation.

It seems to be questionable whether this is a good approach, because the pharmacokinetic behaviour and the estimated PK parameters may depend strongly on the dose level. Therefore, both groups should receive the same dose. If safety is a problem, both groups should receive a dose that is also safe for hepatically impaired subjects.

4. Adjustment of factors which may influence the pharmacokinetic behaviour (p. 4, II.2, 4th paragraph, and p. 6, III.)

It is postulated in section II.2 that the control group should be comparable with the hepatically impaired subjects with respect to age, gender, weight, genetic polymorphisms and with other factors which may influence the pharmacokinetic behaviour of the drug.

So far, a statement is lacking that these factors should also be taken into account in the statistical data analysis (section III). For instance, adjustment for important factors seems to be necessary when modelling the relationship between measures of hepatic function and pharmacokinetic parameters.

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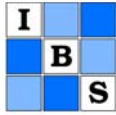
Specific comments:

1. III.1 Parameter estimation (p. 6)

The area under the plasma concentration curve (AUC), the peak plasma concentration (C_{max}) and the terminal half-life ($t_{1/2}$) are considered as important pharmacokinetic parameters. To estimate the terminal half-life for individual subjects it is common to apply log-linear regression to fit the last few observed plasma concentration (this approach is often denoted as noncompartemental method). If this approach is applied it should be postulated in our opinion that the same number of time points (i.e. observed plasma concentrations) should be used for each subject. Otherwise, we would assume different `models' for different subjects.

2. III.2 Presentation of data, descriptive statistics (p. 6, 2nd enumeration, 2nd point)

The pharmacokinetic parameters of interest have usually a log-normal distribution. Therefore, geometric means and / or non-parametric measures (of location and variability) should be provided in addition to or instead of arithmetic means and standard deviations.

3. Appendix (p. 8)

The 'Child-Pugh classification' given in the appendix differs formally from that given in the corresponding FDA document. Change 'Bilirubin (mg/dL)' '2.1-3' ' by Bilirubin (mg/dL)' '2 -3', and 'Prothrombin Time (seconds > control)' '0.3.9' by 'Prothrombin Time (seconds > control)' '<4'.
A classification according to exogenous markers could be added.
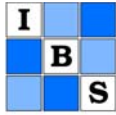
4. Specific comments on wording, misspelling

- Page 3, 5th paragraph, last sentence:

  Change '… increase in bilirubin and prothrombin time.' by '… increase in bilirubin and prolongation in prothrombin time.'

- The abbreviation 'SPC ' should be explained (first mentioned at page 2, enumeration at the top, last point).

- Page 4, last paragraph, 1st sentence, misspelling:

  '…first-pass extraction,…' instead of '… first-pass ex<u>c</u>traction …'

- Page 6, enumeration at top:

  Full stops are missing at the end of the first two points.

- Page 6, III.2,. enumeration:

  Full stop is missing at the end of the first point.

- Page 10, VI. 1st paragraph, last sentence:

  Change the term 'concentration-response relationship' by 'dose- and/or concentration-response relationship'.