April 22, 1999

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Organon Inc.

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

0161 '99 APR 23 A9:15

Docket No. 98D-1195
Draft Guidance for Industry on Bioanalytical
Methods Validation for Human Studies

Dear Sir/Madam:

Reference is made to the document, "Draft Guidance for Industry on Bioanalytical Methods Validation for Human Studies." Availability of this document was announced in the Federal Register on January 5, 1999 (Docket No. 98D-1195).

Attached please find comments regarding the draft document which were generated by colleagues in Europe who are experienced in bioanalytical methods development. We understand that the official comment period for this document has passed. However, while we believe that the draft document is generally good, we are submitting these comments for your consideration, which we believe are relevant and necessary to help clarify and potentially improve specific sections of the guidance.

Should you have questions or wish to discuss particulars regarding the attached comments, please contact the undersigned at (973) 325-4830.

Sincerely,

Thomas L. Pituk

Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

TLP:cs

Sent via Federal Express Airbill # 4101830165

cc: Vinod Shah, FDA
Senior Research Scientist
Office of Pharmaceutical Science (HFD-350)
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857-1706
Federal Express Airbill # 4101830176

Organon

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973) 325-4589

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Comments on "Draft Guidance for Industry on Bioanalytical Methods Validation for Human Studies"

Department of Drug Metabolism and Kinetics
NV Organon
Oss, The Netherlands

Date: 22 April 1999

Contacts: F. Maris, PhD and J. Tonnaer, PhD

Section IV; A. Specificity; page 4; third paragraph

Comment:
During validation of the bioanalytical method for a new chemical entity (NCE) or new biological entity (NBE), it is often not possible, and generally not useful, to check extensively for decomposition products and common OTC drugs and metabolites.

Reason:
For NCEs and NBEs, analytical methods for human plasma/serum are always validated initially prior to first human exposure. At that phase of the development process, decomposition products and metabolites are generally not available or are only available in very limited quantities. Furthermore, the value of checking for decomposition products is questionable because levels of these should be very low (<<5%) in comparison with the parent drug and, consequently, there influence on quantitation of the parent drug is expected to be negligible.
In addition, testing for certain OTC drugs at the exclusion of the many possibilities has very limited practical relevance. Generally a better approach is to analyze a pre-dose sample of the volunteer or patient who participates in the study. Using this approach, if the parent drug is not detected above the level of quantitation, this indicates that there are not other substances present that would affect the analysis.

Section IV; B. Calibration curve; 2. Linearity; page 5;

Guidance text:
"The simplest workable regression equation should be used with minimal or no weighting."

Comment:
In the guidance document, there is no argument given for the recommendation to use minimal or no weighting. Because weighting may in fact be necessary under certain circumstances, it may be helpful if the guidance includes examples of situations in which weighting can be used appropriately. For example, when a method has a wide linear range (e.g., three orders of magnitude), some type of weighting is necessary to accurately quantify the lower calibration points. In addition, the distribution of the QC samples over the linear range in combination with the requirements for the accuracy at each QC concentration, should guarantee sufficiently that the weighting factor selected is appropriate.

Section V; page 10; last sentence of first paragraph

Guidance:
"All study samples from a subject should be analyzed in a single run."

Comment:
While this recommendation represents an ideal situation, for a number of reasons it may be impossible or impractical to analyze all study samples from a subject in a single run. We therefore suggest that this recommendation be revised to "All study samples from a subject should be analyzed in a single run, if possible, whenever practical."

For example, because of the high number of samples in some cases, it is not possible to analyze all samples from one subject in a single run. In addition, in cross-over designs for drug interaction and bioequivalence studies, a significant amount of time can be gained when samples are analyzed after each cross-over period instead of at the end of the study. Using validated methods should guarantee accuracy, regardless of when the samples are run. Based on the validation, the day-to-day variation of the analytical method is known and can be used in the statistical interpretation of the results of the analyses.

Section VI; page 10; Second paragraph

Guidance:
"Reassays should be done in triplicate"

Comment:
Current practice in many labs is to perform reassays in duplicate. Performing reassays in triplicate instead of duplicate requires larger blood sample volumes, which is inconvenient for the study subjects. We propose that the guidance be revised to state "Reassays should be done at least in duplicate."

Section VI; page 12; first bullet point

Guidance:
"Complete serial chromatograms of 20% of subjects, with standards and QC samples"

Comment:
For an average kinetic study, this requirement will lead to about 200 extra pages in the study report. Given the fact that this type of documentation is unlikely to provide meaningful or useful information beyond what would already be expected in the report, we question the need for such a requirement.

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