

FDA DRAFT GUIDANCE

Bioanalytical method validation

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For many years, FDA guidance on bioanalytical method validation issued by the CDER in 2001^[1] was a guiding light for laboratories dealing with the pharmacokinetic analysis of drugs and their metabolites in clinical trials. In September 2013, the agency tabled new draft guidance^[3] on bioanalytical method validation that will have a major impact on the analysis of samples – either drugs or biomarkers – from clinical trials. The guideline includes several new requirements that drugmakers will have to start taking into account.

The basic task in method validation is to investigate the performance of an analytical method before clinical trial samples with unknown concentrations of specific analytes are to be measured. Its core parameters are accuracy, precision, selectivity, sensitivity, reproducibility and sample stability, while further aspects include calibration curves, interference by other substances, specificity etc. These performance parameters have to be tested by each laboratory that offers a specific method used for bioanalytical analysis of clinical trial samples, and summarised in a validation report.

In 2012 the EMA released guidelines on bioanalytical method validation^[2] that are much more explicit and detailed in their requirements than FDA guidance from 2001. While the FDA guidance was primarily written for chromatographic methods, especially LC-MS/MS, the EMA guideline also provided guidance for immunoassays like ELISAs and other ligand binding assays. Despite the increased clarity conferred by the EMA guideline, several aspects of the process remained unclear, including the question of whether biomarker assays have to be validated according to the EMA guideline when they're used for the assessment of pharmacodynamic effects. In September 2013, the FDA then released new draft guidance^[3] on bio-

analytical method validation. It contains several new requirements that may have a serious impact on the analysis of samples from clinical trials.

Impact for surrogate markers

In the draft's very first paragraph, the FDA states that the principles of bioanalytical method validation are not only applicable to the methods used in pharmacokinetic studies (classic bioanalysis) but also in the assessment of biomarkers for the analysis of efficacy or safety. This clear statement removes some uncertainty for sponsors and central laboratories, since neither the EMA guideline nor the FDA guidance from 2001 have claimed any applicability beyond the area of pharmacokinetics. Nevertheless, the EMA and FDA guidelines were often taken as a regulatory basis for method validation studies for biomarker assays in the definition of quality requirements between sponsors and central laboratories. With the new draft guidance, it is now clear that basically all methods that are used for the assessment of safety, efficacy and pharmacokinetics have to be validated according to the same standards. It remains to be seen whether the FDA also regards classic clinical chemistry parameters like amino-transferases or creatinine as safety biomarkers (for liv-



er and kidney function) but it is very clear that biomarkers used for the pivotal determination of safety and/or efficacy need to be analysed with fully validated methods. Often, such biomarkers are analysed using commercially available assays.

Like the EMA guideline, the FDA draft also points out that commercial assays ('kits') need to be validated to the same standards as methods developed by the laboratories that will conduct the analysis of clinical trial samples. Another important requirement relates to the so-called incurred sample reanalysis (ISR): 7% of all analysed samples need to be re-analysed to test reported concentrations for reliability. This applies not only to pharmacokinetic assays but also to biomarker assays, a requirement that goes beyond the standards embedded in the EMA guideline. Although the draft guidance issued by the FDA will likely undergo some revision before final release, it is already obvious that the quality requirements for the acceptance of analytical data from central laboratories have grown more stringent – finally translating into truly outstanding reliability for clinical trial data. ▼

References

- [1] Guidance for Industry, Bioanalytical Method Validation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2001
- [2] EMEA/CHMP/EWP/192217/2009, Committee for Medicinal Products for Human Use (CHMP), Guideline on bioanalytical method validation
- [3] Guidance for Industry, Bioanalytical Method Validation, DRAFT GUIDANCE, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), September 2013

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