The historical development of bioanalytical method validation guidance

Editorial Article

Seda ÜNSALAN*

Istanbul Medipol University, School of Pharmacy, Department of Pharmaceutical Chemistry, Istanbul, Türkiye

A bioanalytical method is a set of procedures involved in the collection, processing, storage, and analysis of a biological matrix for a chemical and biological drug(s) and their metabolite(s). Bioanalytical method validation employed for the quantitative determination of drugs in biological fluids play a significant role in the evaluation and interpretation of bioavailability, bioequivalence, pharmacokinetic and toxicokinetic study data. The quality of these studies is directly related to the quality of the underlying bioanalytical data. It is therefore important that guiding principles for the validation of these analytical methods be established.

Prior to 1990, there were only regulations requiring the bioanalytical methods to be sensitive, specific, accurate and precise. There was a lack of uniformity in conducting validation of bioanalytical method, submission of data to the regulatory agencies and evaluation of the submitted data around the world. As reported in the articles published by Shah (2007) and by Shah and Bansal (2011), the first successful attempt at harmonizing the procedures and requirements for conducting bioanalysis was made in 1990 in a workshop dedicated to bioanalytical method validation. This workshop was co-sponsored by the American Association of Pharmaceutical Scientists (AAPS) and the Food and Drug Administration (FDA). The conference focused on requirements for bioanalytical methods validation, procedures to establish reliability of the analytical method, parameters to ensure acceptability of analytical method performance, method development and method application. The workshop defined essential parameters for bioanalytical method validation — accuracy, precision, selectivity, sensitivity, reproducibility, limit of quantification, and stability — and addressed "how to" evaluate and determine these parameters. In addition to defining various bioanalytical method validation parameters, the workshop discussed appropriate method validation procedures and defined the standard curve, recovery, and replicate analysis. One of the most important outcomes of the first workshop was that it defined "the acceptance criteria for a run". However, the workshop report was not an official document of the FDA. Therefore, the agency decided to develop and publish a draft guidance in January 1999.

*Corresponding author: Seda UNSALAN
E-mail: seda.unsalan@medipol.edu.tr
ORCID: 0009-0007-0668-6161

The second workshop was held in January 2000. The workshop focused on advancements in the field of mass spectrometery and discussed the ligand binding assays. Selectivity issues in ligand binding assays were discussed in detail. Two types of issues must be considered: interference from substances that are physicochemically similar to analyte and interference from matrix components (also termed "matrix effects") that are unrelated to the analyte. And also discussed different categories of validation; Partial Validation, Cross-Validation, and Full Validation. This workshop resulted in the report "A revisit with a decade of progress" and formed the basis for FDA-Guidance for Industry on Bioanalytical Method Validation" in 2001. This guidance was developed largely for the quantitation of small molecules using chromatographic techniques, but applied equally to large molecules and a variety of analytical techniques.

The third workshop discussed the requirements and procedures for bioanalysis using chromatographic or ligand-binding assay was held in May 2006. This workshop clarified the issues related to replacement of quality control samples, determination of matrix effect, use of internal standards and incurred samples reanalysis (ISR). The proceedings of the workshop were published in 2007 (Viswanathan, C. T. et al., Workshop/Conference Report — Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays). The following workshop was held in 2008 and discussed the strategies for conducting ISR. Recommendations concerning the basis for ISR, general operational principles, assessment timing and scope, sample selection, and acceptance criteria were offered. The workshop report was published in 2009 (Fast D, et al., Workshop Report and Follow-Up—AAPS Workshop on Current Topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples—Implications of Crystal City Recommendations).

In September 2013, the FDA released a draft revision of the Bioanalytical Method Validation Guidance, which included a number of changes to the expectations for bioanalysis, most notably the inclusion of biomarker assays and data. To inclusive discussion of the revised draft Bioanalytical Method Validation Guidance, the AAPS and FDA once again collaborated to convene a workshop during early December 2013. This Workshop included discussions on such science-driven topics such as the status of ISR after several years of application, new immunoassay technology, antibody-drug conjugates and the application of Liquid Chromatography Mass Spectrometry protein quantitation. Additionally, the Agency through the guidance and its presentations highlighted areas of additional focus for chromatographic and ligand-binding assays, such as stock solution expiry and most notably, the inclusion of biomarker assays within the Guidance. The workshop report was published in 2014 (Booth B, et al., Workshop Report: Crystal City V—Quantitative Bioanalytical Method Validation and Implementation: The 2013 Revised FDA Guidance) and formed the basis for FDA-Guidance for Industry on Bioanalytical Method Validation in 2018 provided recommendations for the development, validation, and in-study use of bioanalytical methods.

As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines. ICH Guidance "M10 Bioanalytical Method Validation and study sample analysis Guidance for Industry" finalised in 2022 addressed other industry concerns about bioanalytical assays, which are methods used to quantify the analyte(s) and/or their metabolite(s) in biological matrices. This guidance is intended to provide industry with harmonized regulatory expectations for bioanalytical method validation of assays used to support regulatory submissions. Namely to ensure that submissions advance toward the clinical trial phase, it would be necessary to adjust current clinical trial application approaches to the new ICH M10 requirements.