

# Development of Harmonized Bioanalytical Method Validation Guidelines

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## Editorial

Analytical methods play a significant role in the evaluation of drugs and their metabolites in the assessment of pharmacokinetic profile. Since analytical methods and techniques are constantly changing, it is necessary to use well characterized and validated analytical methods to deliver reliable results. Every molecule has its characteristic method of analysis which must be validated based on the long term objective of the analysis. Although, the validation of each of these methods is independent of one another, there are certain conditions that demand the comparison of these methods, such as sample analysis at more than one site using different methods. The comparison of validation of these analytical methods provides inter-laboratory ruggedness. Additionally, it is also essential that the validity of an analytical method be documented before every use such as by constructing a standard curve. However, if the method is used on a regular basis, evidence on its continued validity is routinely provided and repeated validation runs are not required [1].

In May, 2001, the center for drug evaluation and research (CDER) formed and published guidance for industry called Bioanalytical Methods Validation [2]. This guidance provides general guidelines for the validation of bioanalytical procedures such as gas chromatography (GC), high pressure liquid chromatography (HPLC), combined GC and LC mass spectrometric procedures, radio-immuno assay's (RIA) and enzyme linked immuno-sorbent assay (ELISA), for the quantitative evaluation of drugs and/or metabolites in biological matrices such as blood, serum, plasma or urine. This document was compiled under the deliberation of two conferences; (1) Analytical Methods Validation: Bioavailability, Bioequivalence, and Pharmacokinetic Studies (held on December 3-5, 1990) and (2) Bioanalytical Methods Validation: A Revisit with a Decade of Progress (held on January 12-14, 2000).

It was only in the first workshop in December 1990, that procedures required in bioanalytical methods validation were harmonized. Previously, the validation of bioanalytical methods lacked uniformity, which became a challenge for the regulatory authorities to screen. This workshop identified and defined the essential parameters now widely recognized in bioanalytics method validation (BMV), as accuracy, precision, selectivity, sensitivity, limit of quantification, and stability. The major outcome from this workshop was that it identified 'the acceptance criteria for a run' [3]. Based on the widespread acceptance that this workshop received world over, the agency published draft guidance in January 1999.

A year after the publication of the draft guidance, a second bioanalytical workshop was conducted [4]. The main objective of this workshop was to discuss the advances in analytical technology that had occurred over the past decade. The focus was on microbiological and ligand binding assays (LBA) for macromolecules, in which two issues were highlighted; (A) interference from substances that have a physico-chemical similarity to the analyte of interest (such as metabolites), and (B) interference from matrix components that are unrelated to the analyte. In 2003, DeSilva et al published a manuscript which dealt exclusively with the bioanalytical method validation of LBAs for macromolecules [5]. They organized the validation of LBAs life-

cycle into three phases; method development, pre-study validation, and in-study validation, and validate the various parameters, such as specificity, selectivity, linearity, precision and accuracy, in each phase distinctly. This manuscript provides in depth guidelines for analysts dealing with validation of LBAs for macromolecules.

In 2006, the third workshop on BMV essentially revisits the previous manuscripts on small molecule [2] and macromolecule BMV [5] and primarily resolves the acceptance criteria and documentation issues. Recently, there has been an effort to merge the guidelines for chemical and macromolecule analysis validation in 2010 and 2012 by two more workshops, however, a document is yet to be released. On February 1<sup>st</sup> 2012, the European Medicines agency (EMA) published its own set of guidelines which are primarily based upon established fundamentals of the FDA guidance.

A number of studies have been conducted based on the instructions set forth by the guidelines available. A few of them are particularly interesting such as one investigating a novel immunoassay (an ELISA that uses two different monoclonal antibodies for insulin aspart) for insulin aspart, which has the potential of surmounting the limitations of the conventional RIAs used for its quantification thus far [6]. In a different study, Christianson et al have compared and validated a micro flow liquid chromatography (MFLC) coupled to MS/MS, with the conventional LC-MS/MS [7]. Another novel study has validated a method that quantifies the analyte from dried plasma spots on paper substrates, using LC-MS/MS [8]. Studies on molecules such as Amphotericin B [9], and erlotinib [10] in spiked human plasma samples are also based on the same guidelines.

The general consensus is that since the issue of the BMV guidance for industry, differences in approach within the industry have been greatly minimized [3]. However, it is also stated in the document that an alternate approach may be used provided that the necessary validation is performed by the analyst.

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