Update Bioanalytical Methods Prior to Submitting Studies to the FDA

By the latest industry information, it takes an average of 10-15 years from discovery to approval of a new drug, with up to 7 years in clinical development[1]. During this development, many clinical and non-clinical studies will be performed, some with the targeted goal of demonstrating the release profile of the drug and levels of the active and metabolites in the test subjects. Bioanalytical methods are typically used to perform these measurements. In the past there was little reason to worry that during this extended development time the requirements for the supporting bioanalytical methods would change. This is not the case today, and a submission to the FDA may be jeopardized if the supporting bioanalytical methods are not up to the current standards at the time of submission, regardless of their state at the time of use.

The main reason for this change is the activity on the part of the FDA which has established and modified expectations for bioanalytical methods. This started in 2001 when the FDA promulgated *Guidance for Industry Bioanalytical Methods Validation*[2] which was the first specific guidance from the FDA on this topic and gave guidance for both chromatographic and ligand-binding assays used to bioavailability, bioequivalence, and pharmacokinetic studies. However, it did not end there. Since 2001 there have been numerous workshops and the consensus papers published from these workshops have provided *de facto* guidance on the expectation for bioanalytical methods, an example is the one from the 3rd AAPS/FDA Bioanalytical Workshop conducted in May 2006[3].

This means that bioanalytical methods validated in the year 2000 and used to support clinical or non-clinical studies for a product that was eventually filed in 2008, a typical development timeline, may not meet the current FDA requirements. One may seriously question whether the FDA would hold work performed prior to the establishment of the requirements to those same requirements after the fact. The answer lies in the Form 483 issued after an inspection of a contract laboratory in 2009. There were 13 individual observations about bioanalytical methods that were validated and used beginning in 1996 for a drug product that was filed sometime after January 2007. Almost all of the observations relate to inadequacies of the methods according to the current requirements, even though it could be easily argued that by the standards of 1996 (prior to the *Guidance Document*) the methods were adequately validated and applied.

What does this mean to a typical pharma or biotech company? This means that prospectively, you will need to stay on top of changes and developments in bioanalytical methods and ensure that the methods are brought up to date as requirements change. If you have work performed by a contract laboratory, you should not rely upon them to inform you of these changes, but have someone from your organization do this. Before filling, perform a in depth review of all of the methods that support the studies being submitted and ensure that any that require retrospective validation have that performed prior to the filing, or at least prior to any pre approval inspection (PAI).

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[1] *The Drug Development and Approval Process*, John Kelly, M.D., Pharmaceutical Research and Manufacturers of America (PhRMA) website

[2] *Guidance for Industry – Bioanalytical Method Validation*, 2001

[3] *Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays*, Viswanathan, C.T., et al, *AAPSJ*, 9 (2007) Article 4