2018 FDA Bioanalytical Method Validation Guidance Discussion

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EBF Conference, Nov. 23rd 2018

Disclaimer: Bringing forward discussion points from AAPS sub-team/member discussions and internal discussions. Not official position/opinion

What's new in the 2018 BMV Guidance

- The scope is reduced to Chromatography or Ligand Binding Assays. The guidance is no longer applicable to quantitative microbiological procedures.

- The **Chromatographic Methods** (Draft Section III) and **Ligand Binding Assays** (Draft Section IV) have been merged into Section III, Bioanalytical Method Development and Validation, containing 3 subsections; A) Guiding Principles; B) Bioanalytical Parameters of CCs and LBAs; C) Validated Methods: Expectations of In-Study Analysis and Reporting. The merged content captures all the critical parameters and considerations of development, validation, and pre-clinical/clinical study support irrespective of the platform, while highlighting elements unique to either CC's or LBA's.

What's new in the 2018 BMV Guidance

- A subsection, **Dried Blood Spots**, has been created in Section V under Additional Issues for consideration. With the recent development and emergence of the DBS technology as a potential platform to support and replace traditional sample collection techniques, the agency has defined areas of concern to be evaluated during validation and encourages collaboration with FDA early in development.
- Guidance **on additional issues**
  - Biomarkers: Fit for purpose (FFP)
  - Diagnostic Kit/Companion diagnostic device
  - Bridging data from multiple technologies
- The subsections **Documentation for Method Validation and Documentation for Bioanalytical Reports have been merged**. The content captures all critical documentation considerations for validations or bioanalytical reports.

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What's new in the 2018 BMV Guidance

- The **Appendix** has been expanded significantly in the 2018 Guidance Document providing a summary and useful Reference Guide including; A) The expected requirements and acceptance criteria for CC and LBA validations as well as the In-Study Conduct; B) Documentation and reporting requirements at the analytical site during method validation and clinical testing; C) Summary table examples to be included in validation and/or bioanalytical reports.
- Table 1: Detailed recommendation and acceptance criteria for method validation and in-study analysis phase
- Table 2: Detailed recommendation for documentation and reporting for analytical site, validation report and analytical study report
- Table 3: Example of overall summary for validation report and CSR
- Table 4: Example of summary analytical runs for Bioanalytical Study Report

A Big THANK YOU to the FDA Colleagues

Enhanced focus on method development

The purpose of bioanalytical method development is to define the design, operating conditions, limitations, and suitability of the method for its intended purpose and to ensure that the method is optimized for validation.

Before the development of a bioanalytical method, the sponsor should understand the analyte of interest (e.g., determine the physicochemical properties of the drug, in vitro and in vivo metabolism, and protein binding) and consider aspects of any prior analytical methods that may be applicable.

The elements and acceptance criteria of method development and validation are summarized in Table 1. Table 2 describes how the sponsor should document the development and validation of the bioanalytical assay and where it should be stored or submitted.

Method development involves optimizing the procedures and conditions involved with extracting and detecting the analyte. Method development includes the optimization of the following bioanalytical parameters (which are discussed in greater detail in section III.B) to ensure that the method is suitable for validation:

Bioanalytical method development does not require extensive record keeping or notation. However, the sponsor should record the changes to procedures as well as any issues and their resolutions during development of the bioanalytical method to provide a rationale for any changes during the development of the method.

Method Development & Validation

- Section III, Bioanalytical Method Development and Validation, Part A, Guiding Principles
  - Specifically states that "**development does not require extensive record keeping** or notation". The agency then requires the sponsor to provide rationale and capture procedural changes or issues encountered during development of the method. Appears contradictory
  - *Two schools of thought exist within the industry:*

    (1) Assay development is the creative part of the BA projects. Imposing strict guidance/regulation around the practices hinders innovation and /or adds unnecessary burden.

    (2) One might ask how the sponsor could provide any rationale without appropriately documenting all development activities. Also for legal considerations and IP protection sponsor may want to implement throrough documentation.

  - Establish a detailed, written description …The description should identify procedures that control critical parameters in the method (e.g., environmental, matrix, procedural variables) **from the time of collection of the samples** to the time of analysis to minimize their effects on the measurement of the analyte in the matrix

Method Development & Validation

- Section III, Bioanalytical Method Development and Validation, Part B, Bioanalytical Parameters of CCs and LBAs
  - There are no significant changes to the stated expectations for the bioanalytical parameters and acceptance criteria of CC's or LBA's during method validation and in-study sample analysis.
  - *The sponsor should prepare any calibration standards and* **QCs from separate stock solutions**. *However, if the sponsor can demonstrate the precision and accuracy in one validation run using calibrators and QCs prepared from separate stock solutions, then the sponsor can use calibrators and QCs prepared from the same stock solution in subsequent runs. The sponsor should make up calibrators and QCs in lots of blank matrix that is free of interference or matrix effects.*

Fit-for-purpose (FFP) and Regulated Assays

The fit-for-purpose (FFP) concept states that the level of validation should be appropriate for the intended purpose of the study. The key questions listed above should be evaluated relative to the stage of drug development. Pivotal studies submitted in an NDA, BLA, or ANDA that require regulatory decision making for approval, safety or labeling, such as BE or pharmacokinetic studies, should include bioanalytical methods that are fully validated. Exploratory methods that would not be used to support regulatory decision making (e.g., candidate selection) may not require such stringent validation. This FFP concept applies to drugs, their metabolites, and biomarkers.

- **Regulated Studies Support**

The analytical laboratory conducting toxicology studies for regulatory submissions should adhere to 21 CFR 58, Good Laboratory Practices (GLPs).[9] The bioanalytical method for human BA, BE, and pharmacokinetic studies must meet the criteria specified in 21 CFR 320 Bioequivalence and Bioavailability Requirements (i.e., 21 CFR 320.29).

Validation

- Section III, Bioanalytical Method Development and Validation, Part B, Bioanalytical Parameters of CCs and LBAs
- **Section 6, Accuracy, Precision, and Recovery**
  - States the sponsor "***should use freshly prepared calibrators and QCs in all A & P runs. Use of freshly prepared QCs in all A & P runs is preferred: however, if this is not possible, the sponsor should use freshly prepared QC's in one or more A & P runs***".
  - This contradicts the current industry practice. It is unclear if the agency concern is that stability has yet to be validated or some other concern. Warrants discussion and alignment
- **Section 9, Partial and Cross Validations**
  - Specifically highlights the need for partial validation when there is a change to any LBA critical reagent unlike the 2013 Guidance. The agency however, also leaves the sponsor ample room to define the scope of this partial validation by saying: "***can range from as little as one intra-assay accuracy and precision determination to nearly full validation***".

ISR

- Section IV, Incurred Sample Reanalysis
  - The 2013 Draft Guidance (Page 18) had a blanket statement with an expectation that the sponsor would re-test 7% of the Study Sample Size. FDA now recommends (Appendix, Table 1, Page 27, 2018 Guidance) **that 10% of the first 1000 samples and 5% of the remaining samples are re-analyzed**. **The new requirement places an emphasis on the upfront testing as the key performance indication of ISR.**
  - Rare Disease studies that tend to be smaller in size with worldwide recruitment may have to consider the upfront burden.
  - The guidance outlines in very specific detail ISR expectations highlighting the critical priority the agency places on this parameter

ISR for pivotal studies

acceptable to use a frozen curve for the ISR evaluation. The calibration curve, QCs, and study samples for the ISR evaluation should be extracted or processed separately from those used in the original runs. Incurred samples should not be pooled. ISR should be conducted in all studies submitted in an NDA, BLA, or ANDA that provide pivotal data for the approval or labeling of the product, regardless of the matrix. For instance, ISR is expected for all in vivo human BE studies in ANDAs, or all pivotal pharmacokinetic, pharmacodynamic, and biomarker studies in NDAs or BLAs. For nonclinical safety studies, the performing laboratory should conduct ISR at least once for each method and species. Table 1 lists the sample requirements and acceptance criteria for ISR. Written SOPs should be established for the conduct of ISR and to guide an

Endogenous Compounds

- Section V, Additional Issues, Part A, Endogenous Compounds
  - For therapeutic compounds that have an endogenous counterpart, the FDA recommends that the sponsor evaluate parallelism (Bullet point Page 15) in its final guidance.
  - It is noted that the agency does not suggest that parallelism is an absolute requirement, as assessment and determination of such can pose many challenges from any number of sources including matrix and subject to subject variability.

Stability Assessments

- **Whole Blood Stability for sample collection**

Depending on the analyte as well as the sample collection and assay conditions, evaluating the stability of the analyte in whole blood during method development can be useful. For example, a drug can be unstable in whole blood or adsorb to cellular components during collection.

- **Long-term stability**

compared to freshly prepared calibration curves and QCs. Determination of stability at minus 20°C would cover stability at colder temperatures.

Points for Discussion

- Documentation for Method Development
- Fit-for-purpose validation? Full Validation in support of pivotal studies: Discuss to align
- Sample tracking: Clarification of expectation
- Anchor point in calibration curve: Use for curve-fitting as opposed to including in acceptance criteria
- Parallelism: When should it be conducted and how?
- QC: freshly made vs batch made for validation of A&P

Points for Discussion Contd.

- Partial Validation vs Cross-Validation
- Use reference standard close to expiration
- Stability at -20C would cover stability at colder temperature
- Validation should consider potential interfering materials, co-medication etc

Acknowledgements

Members of the PK Assay Sub-team – AAPS

Shire Colleagues

Many other industry & FDA colleagues

EBF and JBF

Endogenous Compounds and Biomarkers (Parallelism Assessment)

- The biological matrix used to prepare calibration standards should be the same as the study samples and free of the endogenous analyte. To address the suitability of using an analyte-free biological matrix, the matrix should be demonstrated to have: (1) no measurable endogenous analyte; and (2) no matrix effect or interference when compared to the biological matrix. The use of alternate matrices (e.g., buffers, dialyzed serum) for the preparation of calibration standards should be justified. The QCs should be prepared by spiking known quantities of the analyte in the same biological matrix as the study samples. The endogenous concentrations of the analyte in the biological matrix should be evaluated before QC preparation (e.g., by replicate analysis). The concentrations for the QCs should account for the endogenous concentrations in the biological matrix (i.e., additive) and be representative of the expected study concentrations.

- Parallelism should be evaluated for assays for endogenous compounds.

- **FFP or full validation assays for biomarkers**

evaluating the safety, activity, or effectiveness of a new medical product, it is critical to ensure the integrity of the data generated by assays used to measure them. Biomarkers can be used for a wide variety of purposes during drug development; therefore, a FFP approach should be used when determining the appropriate extent of method validation. When biomarker data will be used to support a regulatory decision making, such as the pivotal determination of safety and/or effectiveness or to support dosing instructions in product labeling, the assay should be fully validated.