Bioanalytical Method Validation for Biomarkers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Clinical Pharmacology

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Bioanalytical Method Validation for Biomarkers Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance helps sponsors of investigational new drug applications (INDs) and applicants of new drug applications (NDAs), biologics license applications (BLAs), and NDA and BLA supplements as well as abbreviated new drug applications (ANDAs), as applicable, to validate bioanalytical methods used to evaluate biomarker concentrations.[2] This guidance can also inform the development of bioanalytical methods used for the analysis of biomarker concentrations in nonclinical study samples.

The recommendations in this guidance pertain only to the validation of bioanalytical assays to measure in vivo biomarker concentrations in biological matrices such as blood or urine. This guidance does not apply to bioanalytical method validations for the measurement of veterinary drug concentrations or veterinary biomarker concentrations.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time by visiting https://www.regulations.gov and using Docket No. FDA-2017-D-6821. See the instructions in that docket for submitting comments on this and other Level 2 guidances.

[2] This guidance applies to both sponsors of INDs and applicants of NDAs, BLAs, and ANDAs. For the purpose of this guidance, the use of the word *sponsor* applies to both sponsors and applicants.

II. BACKGROUND

The guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022) describing the measurement of concentrations of drugs and biological products in nonclinical and clinical studies was published in its final form in November of 2022.[3] That guidance for industry was developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and was expected to supersede the guidance for industry *Bioanalytical Method Validation* (May 2018), which detailed the elements necessary for method validation of nonclinical and clinical assays of drugs, biologics, and biomarker concentrations in INDs, NDAs, BLAs and ANDAs. However, the *M10 Bioanalytical Method Validation and Study Sample Analysis* excludes biomarkers from consideration. The purpose of this guidance is to address how bioanalytical method validation for biomarkers should be addressed consistent with the principles of the guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022). Upon the publication of this guidance, the guidance for industry *Bioanalytical Method Validation* (May 2018) will be withdrawn.

III. BIOANALYTICAL METHOD VALIDATION FOR BIOMARKERS

Biomarkers are increasingly used to assess the effects of new drugs and therapeutic biological products in patient populations. Biomarkers are important for the successful conduct of nonclinical, biopharmaceutic, and clinical pharmacology studies, as well as safety and efficacy trials. Bioanalytical methods for biomarkers provide data to support the evaluation of safety and effectiveness of drugs and biological products. Therefore, it is important to ensure the integrity of the data generated by these assays.

Biomarkers can be used for a wide variety of purposes during drug development. Therefore, a fit-for-purpose approach should be used when determining the appropriate extent of method validation. For example, when biomarker data will be used to support regulatory decision-making, such as the pivotal determination of safety and/or effectiveness to support approval or to support dosage instructions in product labeling, the assay should be fully validated as described in the guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022). Alternatively, for assays intended to only support internal pharmaceutical company decision-making (e.g., candidate selection, go-no-go decisions, proof-of-concept), the sponsor should incorporate the extent of method validation they deem appropriate.

Validating the analytical method ensures that the data are reliable by addressing certain key questions, including:

- Does the method measure the intended analyte? For example, does anything interfere with the measurement, and is the method specific or selective for the analyte?

[3] FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- What is the variability associated with these measurements? For example, what are the accuracy and precision of the method?

- What is the range in measurements that provide reliable data? For example, what is the sensitivity of the method (e.g., what is the lower limit of quantitation of the method (LLOQ) and upper limit of quantitation of the method (ULOQ))?

- How do sample collection, handling, and storage affect the reliability of the data from the bioanalytical method? For example, what steps need to be followed while collecting samples? Do the samples need to be frozen during shipping? What temperatures are required to store the samples, and how long can the samples be stored? How are samples affected by benchtop manipulations?

Method validation for biomarker assays should address the same questions as method validation for drug assays. The accuracy, precision, sensitivity, selectivity, parallelism, range, reproducibility, and stability of a biomarker assay are important characteristics that define the method. The approach described in the guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022) for drug assays should be the starting point for validation of biomarker assays, especially chromatography and ligand-binding based assays.

The Agency realizes that some of the characteristics or criteria in the guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022) might not be applicable to some biomarker analyses, or that different characteristics should be considered, especially for other types of bioanalytical platforms. Sponsors are encouraged to discuss their plans with the appropriate FDA review division early in development and to include justifications for these differences in their method validation reports.