
Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of New Drugs at CDER-BiomarkerQualificationProgram@fda.hhs.gov, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

**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)**

**December 2018
Drug Development Tools**

Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff

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Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff¹

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I. INTRODUCTION

This guidance for biomarker² development stakeholders and Food and Drug Administration (FDA) staff provides recommendations on general considerations to address when developing a biomarker for qualification under the 21st Century Cures Act (Cures Act) that added new section 507 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Qualification of Drug Development Tools.³ This guidance discusses the evidentiary framework that should be used to support *biomarker qualification*, as that term is now used in section 507 of the FD&C Act, and it was informed by public workshops that predated the Cures Act.

The evidentiary framework described in this guidance identifies the recommended components of a biomarker development program, including determining the type and level of evidence sufficient to support qualification, and addresses how these components interrelate to inform the evidentiary framework. This evidentiary framework is broadly applicable to all biomarker qualification submissions, regardless of the type of biomarker or context of use (COU). Qualification of a biomarker is a determination that within the stated COU, the biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review.⁴ Thus, a qualified biomarker can be used across multiple drug⁵ development programs under the COU for which it was qualified. Requests for qualification of a biomarker should address the evidentiary framework discussed in this document.

¹ This guidance has been prepared by the Office of New Drugs and the Office of Translational Sciences in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration in cooperation with the Center for Biologics Evaluation and Research (CBER).

² Throughout this guidance, the term *biomarker* is intended to include both single entity and composite biomarkers (biomarkers consisting of several individual biomarkers whose measurements are combined in a defined algorithm to reach a single interpretive output). References in this guidance to the use of a biomarker in drug development imply making a decision in drug development based upon the measurement of the biomarker.

³ Section 507 of the FD&C Act (21 U.S.C. 357) was added by section 3011(a) of the Cures Act (Public Law 114-255).

⁴ FD&C Act section 507(e)(7).

⁵ For the purposes of this guidance, all references to drugs or drug products include both human drugs and biological drug products regulated by CDER and CBER, unless otherwise specified.

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34 Many principles discussed in this guidance could also be appropriate when considering the
35 evidence scientifically sufficient to support the use of a biomarker in an individual drug
36 development program (e.g., investigational new drug application, new drug application, or
37 biologics license application submissions). The specifications for medical devices and the
38 processes and evidence that support obtaining marketing authorization for medical devices,
39 including the qualification of a biomarker for use in the investigation of a medical device or use
40 with a medical device, are outside the scope of this document.

41
42 This guidance was informed by several public workshops⁶ that discussed the science to support
43 biomarker qualification; these workshops convened before the enactment of the Cures Act.
44 Development of this guidance was also greatly facilitated by the efforts from the biomarker
45 development community—including FDA, National Institutes of Health (NIH), industry,
46 academia, patient groups, and the nonprofit sector—that developed an October 2016 white paper
47 describing a Framework for Defining Evidentiary Criteria for Biomarker Qualification.⁷ In
48 addition to considering public comments received regarding this guidance, FDA anticipates that
49 the Agency will incorporate additional information required under the Cures Act and discussed
50 in the reauthorized Prescription Drug User Fee Act (PDUFA VI) goals letter (PDUFA VI goals
51 letter)⁸ in a subsequent revised draft version of this guidance. Ultimately, FDA anticipates that a
52 future revised draft guidance on this topic will meet the statutory requirement for draft guidance
53 on a “conceptual framework describing appropriate standards and scientific approaches to
54 support the development of biomarkers” described in section 3011(b)(1)(A) of the Cures Act and
55 meet the commitment in section (1)(J)(6)(d) of the PDUFA VI goals letter related to publishing a
56 draft guidance on “general evidentiary standards for biomarker qualification.” As part of FDA’s
57 efforts to delineate the conceptual framework to support biomarker qualification and the general
58 evidentiary standards for biomarker qualification, FDA also anticipates that subsequent guidance
59 on biomarker qualification will address specific aspects of evidentiary considerations (e.g.,
60 statistical, analytical) in greater detail.

61
62 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
63 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
64 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
65 the word *should* in Agency guidances means that something is suggested or recommended, but
66 not required.

⁶ Workshops convened to discuss the science to support biomarker qualification included: Institute of Medicine Workshop on Biomarker Qualification (2009), FDA co-sponsored Biomarkers Workshop with Howard Hughes Medical Institute (2013), FDA co-sponsored Brookings meeting on Advancing the Use of Biomarkers and Pharmacogenomics (2014), FDA co-sponsored workshop with M-CERSI and the Critical Path Institute on Evidentiary Considerations for Integration of Biomarkers in Drug Development (2015), NIH-FDA Workshop on Biomarker Glossary of Terms (2015), the National Biomarker Development Alliance’s Workshop on Collaboratively Building a Foundation for FDA Biomarker Qualification (2015), and Foundation for the NIH-FDA Workshop on Developing an Evidentiary Criteria Framework for Safety Biomarkers Qualification (2016).

⁷ Biomarkers Consortium Evidentiary Standards Writing Group: Framework for Defining Evidentiary Criteria for Biomarker Qualification. Final version 10/20/2016. Available at:
<https://fnih.org/sites/default/files/final/pdf/Evidentiary%20Criteria%20Framework%20Final%20Version%20Oct%2020%202016.pdf>.

⁸ The PDUFA VI goals letter is available at:
<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>.

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II. BACKGROUND

Historically, biomarkers gained acceptance for use in drug development after evidence from scientific and medical communities accumulated over time, leading to the recognition of the role and value of the biomarker in decision-making. This evidence was considered as part of drug-specific development efforts, and there was no formal regulatory process to assess the broader utility of the biomarker independent from its use in a specific drug program. Even after the Center for Drug Evaluation and Research established the legacy (pre-Cures Act) Biomarker Qualification Program in 2007, progress in biomarker development has been hampered by the lack of a clear, predictable, and specific regulatory framework for the type and level of evidence sufficient to support regulatory decision-making using biomarkers. This guidance is an additional step towards informing future guidances that will specifically address this need, the Cures Act requirements, and PDUFA commitments. Throughout this guidance, FDA uses certain terms that appear in the FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource. The BEST Resource includes a taxonomy of terms that can be accessed online and on which FDA welcomes comment.⁹

III. EVIDENTIARY FRAMEWORK

For a biomarker development effort to be successful, the biomarker should be clearly identified and characterized, including its source material or matrix and its method of measurement. The biomarker should be clearly identified based on the specific analyte (e.g., fibrinogen), anatomic feature (e.g., joint angle), or physiological characteristic (e.g., blood pressure) being measured. For composite biomarkers, it is important to list the individual biomarker components and how these components are interrelated (e.g., a description of an algorithm or scoring system). If individual components have differential weighting, the description should include the biologic rationale to support this decision. Because biomarkers are measured entities, it is important to describe the biomarker source or material for measurement, which determines the biomarker type (e.g., molecular, histologic, radiographic, physiologic characteristic). For example, a molecular biomarker obtained from a biofluid should state the sample matrix (e.g., plasma, urine), and a radiographic biomarker should include the organ or tissue imaged (e.g., kidney). For radiographic biomarkers, it may be appropriate to include the assay/imaging modality or method for interpretation (e.g., dual-energy x-ray absorptiometry, T4/T1 ratio by acceleromyography).

The evidentiary framework that should be considered when determining the type and level of evidence sufficient to support qualification of a biomarker consists of several components. The framework includes: (1) describing the drug development need, (2) defining the COU, (3) considering potential benefits if the biomarker is qualified for use, and (4) considering potential

⁹ The FDA-NIH Biomarker Working Group BEST Resource is available at <https://www.ncbi.nlm.nih.gov/books/NBK326791/>. The BEST Resource contains a glossary intended to harmonize terms used in translational science and medical product development, with a focus on terms related to study endpoints and biomarkers. The glossary will be periodically updated with additional terms and clarifying information (last accessed March 1, 2018).

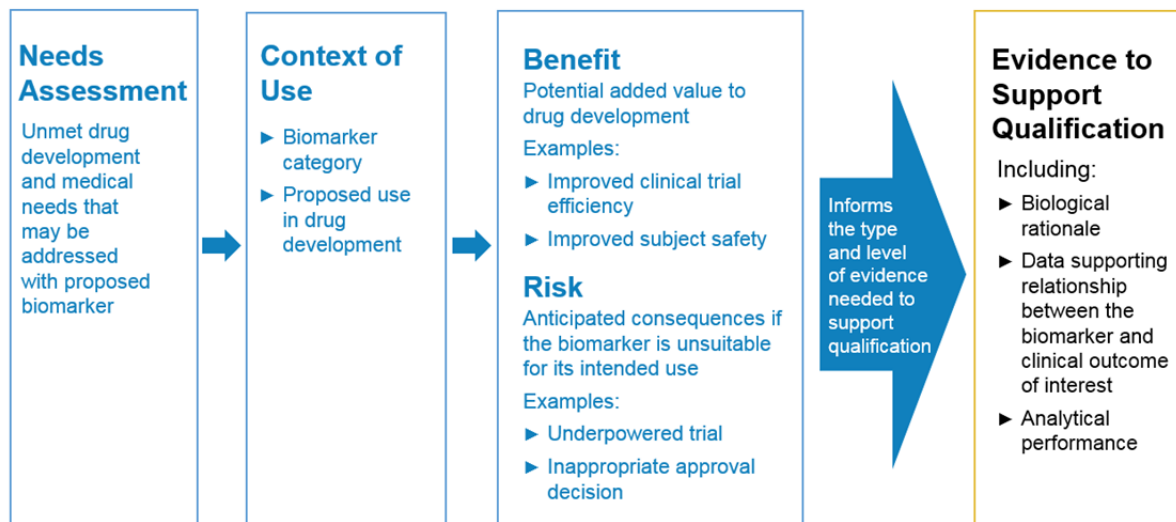
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107 risks associated with the proposed use of the biomarker in a drug development program (see
108 Figure 1).

109
110 **Figure 1: Evidentiary Framework**

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A. Needs Assessment

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116 The needs assessment describes why a biomarker is needed for drug development, including how
117 its use might promote drug development in areas where there is an unmet medical need. The
118 needs assessment should describe the current drug development landscape, such as the use and
119 limitations of available biomarkers or other drug development tools, and the added value the
120 novel biomarker could provide to the current drug development process. The needs assessment
121 should also consider the degree to which there is an unmet medical need in the relevant condition
122 or conditions (e.g., a greater unmet need if there is a serious condition with no or limited
123 treatment) that can be more efficiently or effectively addressed through use of the proposed
124 biomarker in drug development. The needs assessment can include factors that FDA may
125 determine to be helpful for informing FDA prioritization of the review of full qualification
126 packages, including, as applicable, the severity, rarity, or prevalence of the disease or condition
127 targeted by the biomarker; the availability or lack of alternative treatments for such disease or
128 condition; and the identification (by FDA or by biomedical research consortia and other expert
129 stakeholders) of a biomarker and its proposed COU as a public health priority.¹⁰

130
131
132

B. Context of Use

133 According to section 507(e)(4) of the FD&C Act, “the term ‘context of use’ means, with respect
134 to a drug development tool, the circumstances under which the drug development tool is to be
135 used in drug development and regulatory review.” The COU is a concise description of a
136 biomarker’s specified use in drug development. The COU includes two components: (1) the

¹⁰ FD&C Act section 507(a)(2)(C).

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137 biomarker category and (2) the biomarker's proposed use in drug development. Each biomarker
138 qualification effort should identify a single COU.

139
140 Biomarkers can be disease-related or treatment-related and should be classified by the BEST
141 biomarker category, selected from the following (see BEST Resource for discussion of each
142 category of biomarker¹¹):

- 143
- 144 • diagnostic biomarker
 - 145 • monitoring biomarker
 - 146 • pharmacodynamic/response biomarker (e.g., clinical trial endpoints, including surrogate
147 endpoints)
 - 148 • predictive biomarker
 - 149 • prognostic biomarker
 - 150 • safety biomarker
 - 151 • susceptibility/risk biomarker
- 152

153 The *proposed use in drug development* should include, as appropriate:

- 154 • Purpose of use in drug development (e.g., a prognostic biomarker *to support enrichment*
155 *of Alzheimer's Disease clinical study/trial populations*, a safety biomarker *to evaluate*
156 *drug-induced liver injury*)
 - 157 • Proposed stage of drug development (e.g., phase 1 clinical trials, nonclinical safety
158 studies)
 - 159 • Clinical trial population or model system (e.g., healthy adult subjects, patients with
160 COPD, rats, cultured mouse fibroblasts)
 - 161 • Therapeutic mechanism of action (MOA) for which the biomarker is intended to have
162 value, provided that the MOA is relevant to the biomarker's biology and intended utility
163 (e.g., both the MOA and the biomarker are within the same biologic pathway or process)
- 164

165 Accumulating the data to support a biomarker for qualification can take considerable time and
166 resources. Often, requestors do not have adequate data and/or information to support their
167 proposed COU. One approach is to initially qualify a biomarker for a COU that is limited in
168 scope to facilitate the integration of the biomarker in drug development, which could result in the
169 accumulation of additional evidence that can help qualify the biomarker for a COU with a more
170 expanded scope in the future. For example, a biomarker could be qualified first as a
171 pharmacodynamic biomarker for use in dose selection. After additional information is
172 accumulated, the same biomarker could ultimately be qualified as a pharmacodynamic biomarker
173 for use as a clinical trial endpoint; if the biomarker is considered to be reasonably likely to

¹¹ Definition is from the BEST Glossary available at: <https://www.ncbi.nlm.nih.gov/books/NBK326791/> (last accessed March 1, 2018).

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174 predict clinical benefit or has been shown to predict clinical benefit, it could be used as a
175 surrogate endpoint to support accelerated¹² or traditional drug approval, respectively.

176

C. Assessment of Benefits and Risks

177

178
179 Biomarker developers are expected to provide a clear and objective description of the anticipated
180 benefits and risks of the biomarker for the proposed COU, as well as any potential risk
181 mitigation strategies.¹³ The overall balance of benefits, risks, and risk mitigation efforts are
182 critical for determining the strength of evidence sufficient to support qualification.

183

184 The potential benefits of a biomarker for use in drug development depend on the biomarker's
185 proposed COU and the needs assessment. Biomarker use could benefit individual patients
186 participating in clinical trials (e.g., earlier identification of toxicity with a safety biomarker) or
187 general drug development and regulatory decision-making (e.g., a prognostic or predictive
188 biomarker used to enrich a patient population could reduce the sample size needed to achieve
189 statistical significance).

190

191 The potential risks of qualifying a biomarker should address the consequences of incorrect
192 decision-making or harm to patients if the correlation between the biomarker and the outcome of
193 interest does not indicate what it is intended to indicate. Requestors should consider factors that
194 might mitigate harm if the biomarker does not perform as expected. The potential risk is closely
195 linked to biomarker category and the proposed COU. For example, if a safety biomarker fails to
196 accurately predict early toxicity, clinical trial participants might be placed at risk for serious
197 adverse drug reactions. Alternatively, the same safety biomarker might jeopardize the successful
198 development of a promising new drug and prevent significant societal benefits if it erroneously
199 identifies a risk where none exists. These risks could be mitigated, in part, by using the proposed
200 biomarker with existing safety monitoring measures, rather than as a stand-alone assessment for
201 the toxicity of interest. In another example, a prognostic biomarker intended for clinical trial
202 enrichment might fail to identify patients with more rapid disease progression. In this case,
203 mitigation strategies could include incorporating an interim analysis for sample size re-
204 estimation.

205

206 The following questions should be used to characterize the potential benefits and risks of a
207 biomarker for a specific COU:

208

- 209 1. Does the biomarker have the potential to add value to drug development?
- 210
- 211 2. What other tools are available for the biomarker's proposed use and what added value
212 might the biomarker provide?

213

¹² To obtain accelerated approval for a drug, sponsors must meet the statutory criteria in section 506(c) of the FD&C Act (21 U.S.C. 356(c)). Also see 21 CFR part 314, subpart H and part 601, subpart E.

¹³ The terms *benefit*, *risk*, and *risk mitigation* that are used in the context of biomarker qualification have specific meanings that are relevant to biomarker development and evaluation, and these meanings are separate and distinct from how these terms are used in the context of evaluating the safety and effectiveness of medical products.

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- 214 3. What are the anticipated consequences if the biomarker is unsuitable for its proposed
215 use?
216
- 217 4. What factors or other tools can mitigate the potential risks of relying on the biomarker for
218 its proposed use if the biomarker does not perform as expected?
219

D. Determining Evidence That Is Scientifically Sufficient To Support COU

220
221
222 The evidence sufficient to qualify a biomarker depends on its COU and the potential benefits and
223 risks associated with its use. The benefits and risks associated with a biomarker's COU drives
224 expectations for the reliability of the biomarker to predict the outcome of interest. If the
225 potential benefits far outweigh the potential risks and/or there are acceptable risk mitigation
226 approaches, there could be increased tolerance for uncertainty. In such a case, the strength of
227 evidence expected to support qualification could be lower. If the potential benefits minimally
228 outweigh the risks of relying on the biomarker, the strength of evidence expected to support
229 qualification should be higher.
230

231 Ultimately, whether there is sufficient evidence to support qualification of a biomarker for use in
232 drug development depends on the selection of the appropriate biomarker for the proposed COU,
233 the quality of the biomarker measurement, and the correlation of the biomarker with the outcome
234 of interest. Evidence to support qualification consists of data to support clinical validation and
235 analytical validation.
236

237 Clinical validation establishes that a biomarker's relationship with the outcome of interest is
238 acceptable for the proposed COU. The requestor should describe what is known about the
239 biomarker's role in the causal or outcome pathway of interest, as well as describe knowledge
240 gaps about the pathophysiology and molecular underpinnings of the disease. Describing the
241 biomarker's position in the disease pathway, if applicable, helps to support the biological
242 plausibility of the biomarker's role in the proposed COU. The requestor should provide data
243 supporting the relationship between the biomarker and a clinical outcome that reflects how an
244 individual feels, functions, or survives. This relationship should be supported by statistical
245 analyses (see section V.) and should come from multiple independent data sources. Together
246 this information can establish the clinical validity of a biomarker for a specified COU.
247

248 Biomarkers considered for qualification are conceptually independent of the specific method of
249 measurement; however, a biomarker cannot be qualified without a reliable method of
250 measurement.¹⁴ Relevant performance characteristics of the biomarker tests used to support
251 qualification should be assessed through analytical validation studies to ensure that biomarker
252 data for qualification is obtained using acceptable measurement methods to support the proposed
253 COU and that biomarker tests used in drug development for the COU (if different from the tests

¹⁴ Qualification of a biomarker does not connote approval or clearance of a diagnostic device or of a companion or complementary diagnostic device for use in clinical practice, and it also does not qualify the biomarker for use in clinical practice. The approval/clearance of a biomarker test by the Center for Devices and Radiological Health or by CBER also does not indicate qualification of the biomarker for use in drug development.

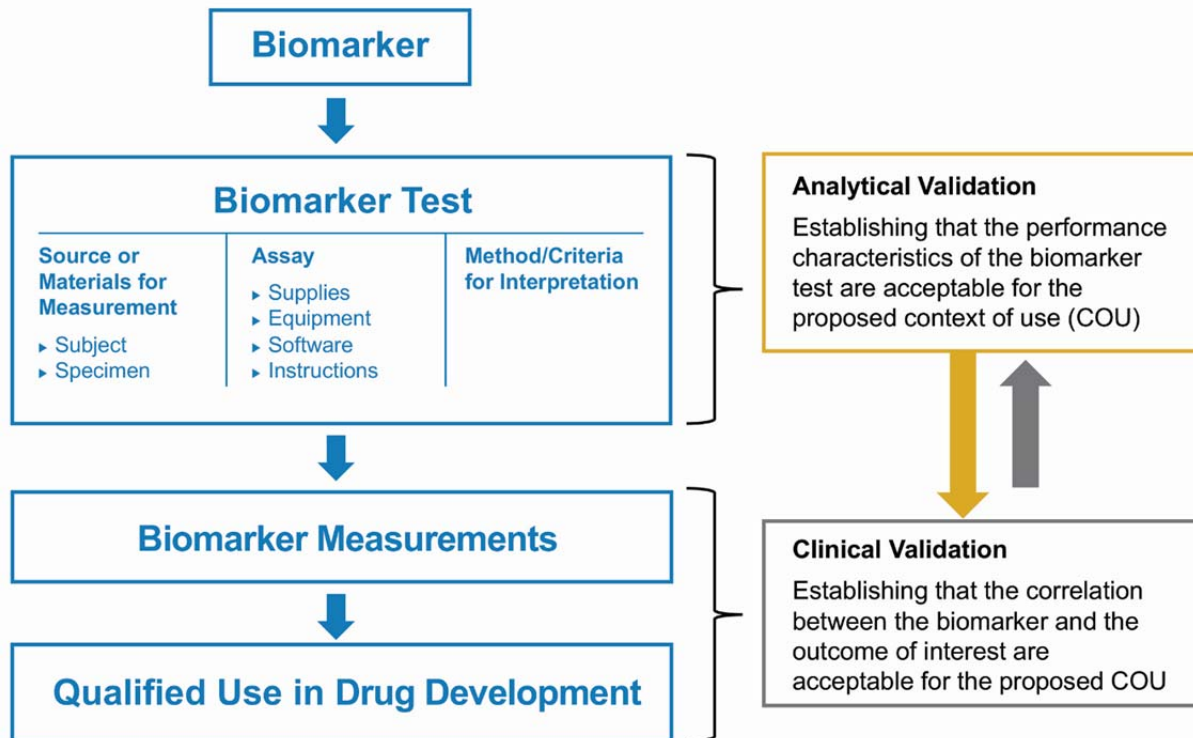
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254 used to qualify the biomarker) perform as well as the tests used for biomarker qualification.
255 Analytical considerations are discussed further in section IV. below.

256
257 Clinical validation and analytical validation are distinct processes; however, the two processes
258 are iterative and dependent on one another. A reliable test should be used to measure the
259 biomarker before the biomarker measurement cutoffs¹⁵ can be established, and the cutoffs should
260 be defined before the biomarker test can be analytically validated. Through this iterative
261 process, experience with the biomarker and the biomarker test could lead to improvements in the
262 technical performance of the test and the understanding of the biomarker's biological and clinical
263 significance. It is important to have a high level of confidence in the biomarker test's analytical
264 performance when confirming the relationship between a biomarker and clinical outcome of
265 interest, and generally, biomarker qualification studies intended to confirm this relationship
266 should be conducted using a validated test (see Figure 2).

267
268 **Figure 2: Biomarker Validation Approach**



269

270 The rigor of the analytical and clinical validation performed for biomarker qualification should
271 support the utility of the proposed COU. A listing of qualified biomarkers with FDA reviews

¹⁵ Cutoff is the value at or above which a biomarker test result is determined to be positive (or in a specific category) and the value below which the result is determined to be negative (or in a different category).

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272 describing the evidence leading to their qualification can be found on the FDA Biomarker
273 Qualification Program website.¹⁶

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275 **IV. ANALYTICAL CONSIDERATIONS**

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277 Because drug development decisions will be made based upon qualified biomarkers, any
278 biomarker test used to measure the biomarker should be robust, sensitive, and specific enough to
279 support the decisions defined by the COU.

280

281 Analytical validation for the purpose of biomarker qualification includes establishing that the
282 analytical performance characteristics of a biomarker test, such as the accuracy and
283 reproducibility, are acceptable for the proposed COU in drug development. This is validation of
284 the test's technical performance, but is not validation of the biomarker's usefulness. The
285 biomarker test and associated performance characteristics will vary depending on the biomarker
286 type (molecular, histologic, radiographic, and physiologic characteristic). A biomarker test is an
287 assessment system comprising three essential components: (1) source or materials for
288 measurement, (2) an assay for obtaining the measurement, and (3) method and/or criteria for
289 interpreting those measurements. All relevant components of the biomarker test should be
290 assessed in the analytical validation studies and determined to be acceptable (see Figure 2).

291

292 Analytical validation of a biomarker test should consider the acceptability of the source or
293 materials from which the biomarker is measured. For a molecular or histologic biomarker, for
294 example, the source includes not only the sample, but also the sample collection, storage, and
295 processing conditions. For a radiographic or physiologic biomarker, the source of measurement
296 could include factors such as the patient preparation and positioning. Sample collection,
297 preparation, and storage protocols (as applicable for the biomarker type) should be established
298 and assessed in the analytical validation studies to determine acceptability.

299

300 A reliable biomarker test is also contingent on all components of the biomarker assay, such as
301 supplies, equipment, software, and instructions. User instructions/protocols should be
302 established and followed during validation testing to ensure acceptability. Additional details
303 such as reagent versions, lot numbers, and software version should be noted to help identify
304 modifications to the test that could alter performance.

305

306 Biomarker measurements are expressed in many ways (e.g., the concentration of molecular
307 species in body fluids, cells, or tissues; the presence or extent of features in images obtained
308 from microscopy or radiology; the magnitude of in vivo physiological signals). Some of these
309 measurements are produced directly from a biomarker test, and others are determined by an
310 interpretation of biomarker test results. Examples of these interpretations include radiographic
311 image analysis and the combination of individual biomarker measurements in a defined
312 algorithm to determine a composite biomarker score. The measurement interpretation, as with
313 the other components of the biomarker test, can introduce error into the biomarker measurement;

¹⁶ Information on qualified biomarkers is available at

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm>.

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314 therefore, reliable and acceptable interpretation should be established in the analytical validation
315 studies.

316
317 Acceptance criteria for analytical performance characteristics for a biomarker test are set
318 according to the overarching specifications for the biomarker to support the proposed COU and
319 according to the risks associated with limitations in the analytical performance of the test.
320 Inadequate biomarker test performance could lead to incorrect interpretation of a biomarker's
321 significance, thus undermining the clinical validation of the biomarker. Bias and dispersion in
322 the biomarker test lead to uncertainty when interpreting biomarker test results and affect the
323 value of the biomarker as a drug development tool. Requestors should consider not only the
324 proposed COU and potential risks and benefits of the proposed biomarker, but also the following
325 factors when specifying performance characteristic acceptance criteria for candidate tests:

- 326
- 327 • The performance characteristics of existing measurement methods
 - 328
 - 329 • The biological variability of the biomarker in the populations of interest, if known
 - 330
 - 331 • The minimum magnitude of biomarker change expected to affect decisions for the
 - 332 proposed COU (i.e., cutoff for separating populations or determining change from
 - 333 baseline)

334 Considerations for assessing the performance characteristics of biomarker tests for specific types
335 of biomarkers are beyond the scope of this guidance. The FDA guidance for industry
336 *Considerations for Use of Histopathology and Its Associated Methodologies to Support*
337 *Biomarker Qualification*¹⁷ provides general considerations regarding performance characteristics
338 for histologic biomarker methodologies. The analytical validation studies and performance
339 characteristics vary greatly according to the technology of the biomarker test. Many well-
340 accepted protocols are published for examination of analytical performance characteristics for
341 specific biomarker test methodologies. Such protocols can be selected and adapted for use in
342 accordance with a risk-based assessment of the evidentiary stringency determined by the
343 proposed COU.

344 345 **V. STATISTICAL CONSIDERATIONS**

346
347 The goal of statistical analyses in biomarker qualification is to evaluate the degree and certainty
348 of association between a biomarker and an outcome of interest. Consideration should be given to
349 the design and conduct of studies contributing data to support biomarker qualification, as well as
350 the statistical analyses conducted. This section describes the potential sources of data, as well as
351 study design and statistical considerations when assessing the association between a proposed
352 biomarker and an outcome of interest for the purposes of biomarker qualification.

353
354 Data used to establish the relationship between a biomarker and an outcome of interest, to
355 support biomarker qualification, can come from a variety of sources including the following:

¹⁷ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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- Randomized controlled trial
- Single-arm/historical control trial
- Cohort study
- Case-control study (including nested)
- Cross-sectional study
- Case series or case reports
- Registry information
- Meta-analysis

The strongest level of evidence to support the association of a biomarker with an outcome of interest comes from prospective studies that are specifically designed and powered to assess the association. In many settings, however, data from studies conducted for other purposes are used to support biomarker qualification. Ultimately, the COU, with its associated potential benefits and risks, determines what types of data may be acceptable to support qualification; clinical trial data is not critical for all COUs. Regardless of the data sources proposed to support the biomarker’s COU, biomarker developers should consider the potential methodological limitations that could lead to overestimation of any actual associations, including lack of proper control for bias, confounding, and multiplicity, and address these limitations in their analysis plan. Verification of the results with an independent data source increases the credibility of the results.

Although the recommendations provided in the ICH guidance for industry *E9 Statistical Principles for Clinical Trials*¹⁸ are primarily intended for late-stage interventional clinical trials, many of the principles described in ICH E9 are also relevant when considering the data intended to support biomarker qualification. Specifically, the principles are as follows:

- To the extent possible, the sample size should be sufficient to ensure adequate power to assess a clinically relevant association between the biomarker and the outcome of interest with reasonable dispersion. Sample-size considerations could be based on a single study or multiple studies considered in aggregate, and it is recognized that flexibility might be needed in certain clinical contexts (e.g., rare diseases).
- The analysis plan should control for multiplicity and consider the potential for false positive results. Multiplicity commonly occurs when analyzing multiple-candidate biomarkers and could lead to overestimation of biomarker associations with the clinical outcome of interest.
- The strength of the relationship between the biomarker and the outcome of interest should be quantified appropriately. Over-reliance on p-values should be avoided.

¹⁸ Available on the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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- Potential sources of bias should be identified and strategies to minimize bias should be described. For example, when possible, the biomarker analysis plan should be developed before unblinding of the data and access to subjects' biomarker status for purposes of the analysis. In some situations, clinical outcome data might have already been unblinded and analyzed, but the initial analyses did not include the biomarker data (i.e., if samples were collected for later use) or the analyses recommended to support qualification were not performed. Although such data could be used to support qualification, the analyses intended to support biomarker qualification should be specified in an analysis plan with a prospective-retrospective design before analyzing the data.
 - Consideration should be given to sample and data collection methods, including strategies to minimize and account for the effect of missing data, and these methods should be included in the analysis plan. When collection of biomarker data is only from a subset of clinical sites, groups, or treatments, this non-randomized sampling (convenience sampling) might be statistically problematic if the subset is somehow partial to the outcomes being studied, yielding biased estimates with unknown characterization of the bias.
 - Innovative statistical approaches such as adaptive designs and Bayesian designs, including prior information and hierarchical models, can be considered for qualification of biomarkers.
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418 Data supporting biomarker qualification are often based in part on the published literature and, in
419 some situations, could be exclusively based on the published literature. It is critical for the
420 biomarker developer to identify the limitations and gaps in these data and address how they
421 affect the interpretability of the results. In addition, when using published literature, the criteria
422 for study inclusion should be specified a priori in a systematic study protocol of the published
423 literature, to avoid publication or selection bias.

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425 When assessing whether the association between a biomarker and an outcome of interest is
426 acceptable for the proposed COU, a key consideration is how to define the outcome of interest.
427 In some settings, there might not be a current standard outcome, or a standard outcome with
428 known limitations is used for comparative purposes. For example, changes in serum creatinine
429 are widely used in biomarker development as the current standard for predicting drug-induced
430 kidney injury. However, changes in serum creatinine levels are neither highly sensitive nor
431 highly specific for drug-induced kidney injury. In a setting in which the current standard
432 outcome has significant limitations or a current standard outcome does not exist, it is important
433 to consider the totality of all available data that may provide sufficient support to establish that
434 the biomarker can be acceptably relied upon for the proposed COU. Each biomarker
435 qualification submission has unique challenges that call for careful clinical and statistical
436 considerations that may lead to distinct solutions.

437

438 There are multiple statistical approaches to assessing the association between a biomarker and
439 clinical outcome measures. For binary outcome measures, such as the presence or absence of
440 disease, results can be evaluated using clinical sensitivity and specificity, and positive and
441 negative predictive values, or by evaluating receiver operating characteristic curves. For

Contains Nonbinding Recommendations

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442 continuous outcome measures, such as disease progression, results can be evaluated using
443 regression models. When appropriate, adjusted or composite biomarkers can be considered with
444 adequate justification, including biomarkers derived from composite measurements, covariate-
445 adjusted measurements, change from baseline measurements, and repeated measurements.
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447 When continuous data will be dichotomized, the relationship between the clinical outcome and
448 the biomarker could be initially established quantitatively. Expressing biomarker measures
449 quantitatively increases the statistical power compared to dichotomization when establishing
450 such a relationship. Once a relationship between a biomarker and an outcome of interest has
451 been established, several cutoffs on a continuous biomarker can be considered. The most
452 appropriate cutoffs can then be selected by comparing the clinical outcomes of *at risk* subjects
453 with each different biomarker cutoff. The choice of a cutoff can also be informed by the benefit-
454 risk tradeoff of the decisions made based on the biomarker and the proposed COU (e.g., selecting
455 a cutoff that gives more weight to clinical sensitivity versus a cutoff that gives more weight to
456 clinical specificity). In some instances, selecting a specific cutoff might not be appropriate, and
457 describing a spectrum of threshold values for the biomarker could be more informative. For
458 example, in the case of an enrichment biomarker, submissions might describe a spectrum of
459 cutoffs in a model representing the potential increase in power to be gained from enrichment,
460 which should be considered against potential enrollment challenges resulting from a narrowed
461 patient population.
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463 There are no set quantitative criteria for determining whether the relationship between the
464 biomarker and the clinical outcome is sufficiently strong to support biomarker qualification.
465 Criteria based on parameters used to quantify the relationship, such as the threshold values for
466 sensitivity and specificity, and the presence of a gradient (e.g., clinical performance change as
467 function of biomarker quantity) can provide confidence that a finding is likely to be relevant,
468 reliable, and statistically robust. Additional considerations that support the biomarker's
469 association with the clinical outcome should also be assessed, such as whether there is a strong
470 biological rationale supporting the role of the biomarker in the proposed COU and whether the
471 findings are supported by more than one investigation or analysis set or there are multiple lines
472 of evidence (e.g., experimental models and human studies). Together, the strength of the data
473 supporting the association and additional considerations should be evaluated to determine
474 whether the evidence supporting the relationship between the biomarker and the clinical outcome
475 is adequate to support biomarker qualification. This determination will be dependent on the
476 evidentiary framework assessment for each individual submission described in section III.