
Guidance for Industry

E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions

**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)**

**August 2011
ICH**

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1, 1.2)²

The guidance describes recommendations regarding context, structure and format of regulatory submissions for qualification of genomic biomarkers (as defined in ICH E15³). Qualification is a conclusion that, within the stated context of use, the results of assessment with a biomarker can be relied upon to adequately reflect a biological process, response, or event, and support use of the biomarker during drug or biotechnology product development, ranging from discovery through postapproval. A biomarker qualification application might be submitted to regulatory authorities if the biomarker directly or indirectly helps in regulatory decision-making.

FDA's guidance documents, including this guidance, 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

¹ This guidance was developed within the Efficacy Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, August 2010. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

² Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, August 2010.

³ ICH *E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* defines a *genomic biomarker* as a "measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions."

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

A. Objectives (1.2)

The objective of the guidance is to create a harmonized recommended structure for biomarker qualification applications that will foster consistency of applications across regions and facilitate discussions with and among regulatory authorities. It will also reduce the burden on sponsors as a harmonized format will be recommended for use across all ICH regulatory regions. It is also expected that the proposed document format will facilitate incorporation of biomarker data into specific product-related applications. Biomarker qualification can take place at any time during drug or biotechnology product development, ranging from discovery through postapproval. For those instances where it is appropriate, general guidance for inclusion of biomarker qualification data into the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) format for marketing authorization applications is provided in this document. The use of the CTD format would be considered appropriate when biomarker data are submitted as part of a new drug application (NDA), a biologics license application (BLA), a market authorization application (MAA), or other postapproval regulatory procedures, or upon request by the regulatory authorities.

B. Background (1.1)

The use of biomarkers has the potential to facilitate the availability of safer and more effective drug or biotechnology products, to guide dose selection, and to enhance their benefit-risk profile. This guidance is based on previous experiences with submissions containing biomarker data in the various regions. These submissions have been either stand-alone biomarker qualification applications or a component of medicinal product-related regulatory process marketing applications (NDAs/BLAs/MAAs). The development of a consistent format for submission of biomarker data will facilitate easy review and exchange of assessments between regions.

C. Scope (1.3)

The scope of this guidance is the context, structure, and format of qualification submissions for clinical and nonclinical genomic biomarkers related to development of drug or biotechnology products including translational medicine approaches, pharmacokinetics, pharmacodynamics, and efficacy and safety aspects. A qualification submission can include data and claims for a single genomic biomarker, or for multiple genomic biomarkers used as classifiers. While this guidance does not explicitly cover nongenomic biomarkers, the principles described in this document are applicable to a variety of biomarker categories (e.g., genomics, proteomics, imaging) and other qualification contexts associated with drug or biotechnology product development. A qualification submission for a combination of biomarkers (e.g., genomic together with nongenomic biomarkers) is also possible. Unless otherwise specified, we will use the generic term *biomarker* throughout the remainder of this document.

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The guidance also covers the submission of data relevant to the validation of new analytical approaches to improve the evaluation of current biomarkers. This guidance does not address either the qualification process or the evidentiary standards for a biomarker to be qualified by regulatory authorities.

II. GENERAL PRINCIPLES (1.4)

The proposed context of use of a biomarker corresponds to the data supporting its qualification. The proposed context of use should be clearly detailed in the submission package. Reference should be made to the specific use of the biomarker in drug or biotechnology product development. The context of use of a biomarker in a biomarker qualification can be narrow or broad: the biomarker(s) might be useful for only a single drug or biotechnology product, for several drug or biotechnology products in a drug class, or even across several drug classes.

The structure of the submission should be consistent, regardless of the context proposed, and flexible enough to deal with the specific attributes of each submission. In addition, use of the recommended structure should facilitate submission and review of future biomarker qualification submissions expanding the use of the biomarker to new contexts, as would be the case, e.g., if a nonclinical context of use expands to a clinical context of use.

The format of the data for qualifying a biomarker can vary significantly depending on the context. It is therefore only possible to provide general guidelines on data format for a biomarker qualification submission. The format should support an evaluation of the data and can include reports, tabulations, and raw data (if requested by regulatory authorities according to the relevant practices in place). Data format should be consistent with the methodology and platform used for analyzing the biomarker in question. Reference to standards and/or accepted methods used should be described as applicable.

The dossier structure described in this guidance is intended for biomarker qualification submissions after sufficient supporting data have been generated. However, this structure can also be considered for submissions intended to obtain scientific advice from regulatory authorities before or during the generation of the biomarker data intended to support qualification.

The recommended biomarker qualification submission is aligned with the CTD format to facilitate submission and review. The proposed overall organization of the biomarker qualification submission described herein corresponds to the CTD format, which consists of five parts (Modules 1-5). The sections of the biomarker qualification submission and their corresponding CTD sections are as follows:

- ICH E16 Section 1 (Regional Administrative Information) corresponds to CTD Module 1 with specific information on the qualification procedures;
- Section 2 (Summaries) corresponds to CTD Module 2;
- Section 3 (Quality Reports) corresponds to CTD Module 3;

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- Section 4 (Nonclinical Study Reports) corresponds to Module 4; and
- Section 5 (Clinical Study Reports) corresponds to Module 5.

More details are described in the ICH M4 and other relevant guidances. Applicants who wish to submit in accordance with the Electronic Common Technical Document (eCTD) format should also consult the ICH M2 guidance (Electronic Standards for Transmission of Regulatory Information) and other relevant guidances, as well as national and regional laws, regulations, and recommendations.

To facilitate the integration of biomarkers in global drug or biotechnology product development it is recommended that qualification submissions be submitted simultaneously to pertinent regulatory authorities. It should be noted that if a biomarker has already been endorsed as qualified by a regulatory authority, biomarker data generated within the qualified context of use do not need to be re-submitted to the authority for re-qualification in an NDA/BLA/MAA. It would be appropriate to simply provide a copy of the assessment report of the authority in the NDA/BLA/MAA or other relevant regulatory procedure.

III. STRUCTURE OF BIOMARKER QUALIFICATION SUBMISSIONS (2)

The biomarker qualification submission should include the following sections:

Section 1: Regional Administrative Information

Section 2: Summaries

- Biomarker Qualification Overview

Introduction, proposed context of use, high-level data description, integrated critical appraisal of the data/methods, additional data needed from ongoing or planned studies, and justification for the proposed context of use.

- Overall Summaries of the following (if appropriate):
 - Analytical Assay Data
 - Nonclinical Biomarker Data
 - Clinical Biomarker Data

If included in an NDA/BLA/MAA, the contents in Section 2 should be converted into chapters in the appropriate CTD Module 2 such as Overview(s) and/or Overall Summary(ies).

Section 3: Quality Reports

- Structural, manufacturing, and quality characteristics of investigational drug(s) for the biomarker qualification studies (as applicable).

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Such information is not expected to be included in a stand-alone biomarker qualification submission, independent from an NDA, BLA, or MAA.

Section 4: Nonclinical Reports

- Analytical assay development reports⁴
- Analytical assay validation reports²
- Nonclinical study reports (in vitro)
- Nonclinical study reports (in vivo, specify species)

Section 5: Clinical Reports

- Analytical assay development reports⁵
- Analytical assay validation reports³
- Clinical pharmacology study reports
- Clinical efficacy and/or safety study reports

The recommended content of these sections is explained in more detail below.

A. Section 1: Regional Administrative Information⁶ (2.1)

This section should contain documents specific to each region, for example application forms and/or cover letter. The content and format of this section can be specified by the relevant regulatory authorities.

B. Section 2: Summaries⁷ (2.2)

By analogy to the CTD structure, biomarker qualification submissions should contain a Biomarker Overview to discuss and interpret the strengths and limitations of the submitted data. It should be supported by the separate technical, preclinical and clinical data summaries, which should present the study data as a detailed factual summarization in text, tables and figures.

1. Biomarker Qualification Overview (2.2.1)

a. Introduction (2.2.1.1)

⁴ Corresponds to CTD Module 4 section 4.2 or 4.3

⁵ Corresponds to CTD Module 5 section 5.3

⁶ Corresponds to CTD Module 1

⁷ Corresponds to CTD Module 2

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This section should be concise. It can include a description of the disease and/or experimental setting, the definition of the biomarker (e.g., in the case of genomic biomarkers, whether a single nucleotide polymorphism (SNP), copy number variation (CNV), or differential gene expression signature) and a rationale for the biomarker's use in drug or biotechnology product development, from discovery through postapproval.

It should summarize the key characteristics of the biomarker, including;

- strengths and limitations (e.g., comparison with relevant standard methods where available, presence/absence of information on pertinent species/population)
- whether it is a single or composite biomarker; if it is a composite biomarker, its component markers and the process through which these were selected should be defined
- objective and design of the studies supporting its use, such as prospective versus retrospective study design, study comparators and sample size

A summary of the proposed context of use of the biomarker should be provided in this section. More details, including the full context of biomarker use, should be described in the next section.

b. Context of Use (2.2.1.2)

The elements describing the context of use for a biomarker should include (1) the general area, (2) the specific biomarker use, and (3) the critical parameters that define when and how the biomarker should be used. The context of use can be limited to use in drug or biotechnology product development. It is expected that a biomarker proposed for qualification would facilitate drug or biotechnology product development program(s) or drug or biotechnology product use and could offer an improvement over currently available biomarkers or safety or efficacy endpoint assessments.

The proposed context of use for a biomarker should be supported by data that are available in the initial qualification dossier submission. If the reviewing authority identifies an inconsistency between the proposed context and the data, additional data can be provided during the qualification processes, if the authority agrees.

The context of use can be described according to the following taxonomy (see examples below):

General Area (including, but not limited to)

Nonclinical/Clinical

- Pharmacology
- Toxicology
- Efficacy
- Safety
- Disease

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Specific Biomarker Use(s) Biomarkers can be used for a wide range of purposes, including, but not limited to, the following examples:

- Patient/clinical trial subject selection
 - Inclusion/exclusion criteria
 - Trial enrichment or stratification
- Assessment of disease state and/or prognosis
- Assessment of mechanism of action
 - Mechanism of pharmacological mode of action
 - Mechanism of therapeutic effect
 - Mechanism of toxicity/adverse reaction
- Dose optimization
 - No observed effect level (NOEL) in animal models
 - No observed adverse effect level (NOAEL) in animal models
 - Algorithm-based dose determination (quantitative algorithmic dosing)
 - Determination of likely dose range
- Drug response monitoring
 - Monitoring drug safety
 - Monitoring drug efficacy
- Efficacy maximization
 - Indicating/predicting drug efficacy
- Toxicity/adverse reactions minimization
 - Indicating/predicting toxicity/adverse reactions
 - Detecting/monitoring onset/reversibility of toxicity/adverse reactions

Critical Parameters of Context of Use (including, but not limited to)

- Drug or biotechnology product-specific use/drug class-specific use/use not linked to specific drug or biotechnology products or drug classes
- Disease diagnosis and phenotypes, prognosis, or stage
- Sample collection
- Assay specifications
- Tissue or physiological/pathological process
- Species
- Demographics, including ancestry and/or geographic origin
- Environmental factors

Examples of Context of Use for Biomarkers

A biomarker measurement could apply to more than one context of use, depending on the general area and/or specific use within a single submission, as shown in the following examples of genomic biomarkers. While hypothetical examples for genomic biomarkers are depicted here, the principles for context description are applicable for all types of biomarkers submitted for qualification.

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(i) *Nonclinical Safety*

Messenger RNA levels of kidney injury molecule 1 (*Kim-1*) and clusterin (*Clu*) can be included as genomic biomarkers of drug or biotechnology-induced acute renal tubular toxicity in rat toxicology studies. The context of the submission in the biomarker qualification application would be defined as follows:

- *General Area*: nonclinical safety and toxicology
- *Specific Biomarker Use*: assessment of mechanism of toxicity and dose optimization (NOAEL) in animal models
- *Critical Parameters of Context of Use*:
 - Drug or biotechnology product-specific use: ***no***
 - Assay specifications: ***mRNA***
 - Tissue or physiological/pathological process addressed: ***kidney***
 - Species: ***Rattus norvegicus***

(ii) *Clinical Pharmacology/Drug Metabolism*

CYP2C9 genetic polymorphism produces poor metabolizer (PM) and extensive metabolizer phenotypes and differences in Drug A exposure. Plasma levels of Drug A in patients/clinical trial subjects who are known to be CYP2C9 PMs are increased due to reduced metabolic clearance. Context of the submission in the biomarker qualification application would be defined as follows:

- *General Area*: Clinical Pharmacology/Drug Metabolism and Safety
- *Specific Biomarker Use*: patient/clinical trial subject selection (inclusion/exclusion criteria, trial enrichment or stratification), dose optimization in individual patients and predicting adverse reactions/risk minimization
- *Critical Parameters of Context of Use*:
 - Drug or biotechnology product-specific use: ***Drug A***
 - Assay specifications: ***Genotyping***
 - Species: ***Homo sapiens***
 - Demographics including ancestry and/or geography: ***population-specific allele frequency***

(iii) *Clinical Safety*

The *HLA-B*1502* allele is associated with an increased risk of the development of Stevens-Johnson Syndrome following administration of Drug B in Han-Chinese.

- *General Area*: clinical safety.
- *Specific Biomarker Use*: patient selection (inclusion/exclusion criteria), predicted safety and mechanism of adverse reaction/toxicity
- *Critical Parameters for Context of Use*:
 - Drug or biotechnology product-specific use: ***Drug B***
 - Assay specifications: ***Genotyping***
 - Species: ***Homo sapiens***
 - Demographics including ancestry and/or geographic origin: ***Han-Chinese***

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c. Summary of Methodology and Results (2.2.1.3)

This section should provide a high level summary of methods and results across studies, using tabular representations and figures as applicable. The review should be followed by a critical assessment and appraisal of overall results, including discussion and interpretation of the findings with regard to the proposed context. It should present and discuss the strengths and limitations of the biomarker qualification program and study results, analyze the benefits of the biomarker for its context, and describe how the study results support its use in the proposed context.

Important observations regarding the source of data, identified deficiencies, and a brief overview of how they relate to the proposed context and how they could be addressed in future submissions should be included. Additionally, key topics identified for discussion should be mentioned.

d. Conclusion (2.2.1.4)

The conclusion should:

- Provide an assessment of expected benefits for the application of the biomarker based upon results of relevant studies, including interpretation of how the biomarker performance supports its use in the proposed context;
- Address issues encountered during the biomarker qualification studies, explaining how they have been evaluated and resolved;
- Identify unresolved issues, and explain why they should not be considered barriers to qualification for the proposed context of use and/or describe plans to resolve them, if applicable.

2. *Data Summaries (Analytical, Nonclinical, Clinical; as appropriate) (2.2.2)*

The data summaries should include a detailed factual summarization of information from the analytical (assay development) or any additional technical information, nonclinical or clinical studies (as appropriate), including integrated analysis of the biomarker qualification studies and individual study synopses. These should provide results across studies, using tabular representations or figures as applicable.

To achieve these objectives, this section should:

- Describe and explain the overall approach to the biomarker qualification program including (1) methods and relevant aspects of study design, (2) technical and biological replication, and (3) statistical analysis, including hypothesis statements, endpoints, and justification for sample size. Describe the rationale for the selection of the population sample studied in the biomarker qualification and discuss constraints derived from this selection, such as those associated with ethnicity or disease state;
- Contain criteria for determining sample suitability (e.g., type, amount and/or age of specimen, DNA yield);

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- Describe the analytical performance characteristics of the assay (e.g., for in vitro assays, accuracy, precision, and other standard parameters) including any specific recommendations where applicable on sample handling, storage, and quality requirements;
- Describe the results supporting the nonclinical/clinical use of the biomarker (e.g., retrospective/prospective correlation with phenotype/outcome).

The use of graphs and tables in the body of the text is encouraged to facilitate the regulatory review process. It is suggested that material presented fully elsewhere not be repeated in this section; rather, appropriate cross-references to more detailed presentations provided elsewhere in the study reports and other documents (Section 4 and 5) are encouraged.

- Individual study synopses (2.2.2.1)

This section should provide synopses of the individual studies included in the qualification dossier. Where the submission is based primarily on scientific publications, abstracts and key tables taken from the scientific publications can be used for this section; these should summarize information obtained from each of the studies for which reports and/or manuscripts have been included in Sections 4 and 5. The length of these sections can vary according to the information to be conveyed.

C. Section 3: Quality⁸ (2.3)

Drug or biotechnology product quality and manufacturing data would not be expected in a stand alone biomarker qualification submission independent from an NDA, BLA, or MAA.

D. Sections 4⁹ (Nonclinical) and 5¹⁰ (Clinical) (2.4)

In these sections, full study reports for biomarker qualification should be provided, and raw data made available to the regulatory authorities upon request. Information on compliance with Good Clinical Practices (GCP) can be included in these sections. The study reports can follow relevant ICH guidances (e.g., E3, E15, M4E, M4S)¹¹ where appropriate for their preparation. Within the study reports, the appropriate format of the data will depend on the characteristics of the biomarker measured (e.g., for genomic biomarkers, SNPs, and/or CNV) and the methodology used (e.g., for genomic biomarkers, microarray and/or Polymerase Chain Reaction).

⁸ Corresponds to CTD Module 3

⁹ Corresponds to CTD Module 4

¹⁰ Corresponds to CTD Module 5

¹¹ ICH *E3 Structure and Content of Clinical Study Reports*; *E15* (see note 4); *M4E The CTD — Efficacy*; *M4S The CTD — Safety*.

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Regardless of the biomarker investigated or technology used, the rationale for selection of the population sample (e.g., species, age, sex) and of other variables related to the phenotype studied should be clearly described. Study reports used to generate the biomarker qualification data should specify critical variables including, but not limited to, the following examples:

- The number and classification of patients/clinical trial subjects who participated in the biomarker study, and the number and classification of patients/clinical trial subjects with assessable biomarker data.
- Performance characteristics of the biomarker test used, based on retrospective and/or prospective correlation with nonclinical and/or clinical endpoint data. These reports should include a description of the methods and study designs as well as the results of any functional studies performed.
- Variables that might both impact on the validity of the assay chosen and contribute to interpretation of results:
 - Hardware or platform used
 - Current internationally recognized standards for the chosen technology
 - Clinical variables that might contribute to interpretation of results such as food, exercise, measurement schedule
- Methods and software used for analyses of raw data.

As an example, in the case of genomic biomarkers, additional critical parameters could also include:

- Criteria for determining sample quality (e.g., age of specimen, DNA yield)
- Methods used for determination of gene expression or DNA sequence and other structural characteristics including modified DNA bases (e.g., epigenetic marks such as 5-methylcytosine)
- Criteria used for selection of candidate genes, if this is the chosen approach (candidate by position, by function, based on expression profiling data)
- Results of analyses of genomic biomarkers, all of which should be described, as applicable, to current internationally recognized standards

Copies of other documents supporting the biomarker qualification submission should be provided in Section 4 for nonclinical information or Section 5 for clinical information. This includes, but is not limited to, copies of reference material relating to Sections 2, 4, and 5. This reference material can include, but is not limited to, the following:

- Published articles in peer-reviewed journals (including meta-analyses)
- Expert statements regarding the utility of the biomarker(s) issued by academic or commercial institutions, patient organizations, public-private consortia, and medical practice oversight boards providing guidance on such utility
- Evaluation reports or other relevant documents as issued by regulatory authorities (e.g., report of relevant scientific advice)
- Manufacturer's technical description of commercially available biomarker assays (if appropriate)

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IV. ABBREVIATIONS (3)

BLA – biologics license application (FDA)

CNV – copy number variation

DNA – deoxyribonucleic acid

MAA – market authorization application (EMA)

NDA – new drug application (FDA) and Japanese new drug application (MHLW/PMDA)

NOAEL – no observed adverse effect level

NOEL – no observed effect level

PM – poor metabolizer

RNA – ribonucleic acid

SNPs – single nucleotide polymorphisms