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Genomic Biomarkers Related to Drug Response:
Context, Structure and Format of Qualification Submissions

Step 3

NOTE FOR GUIDANCE ON GENOMIC BIOMARKERS RELATED TO DRUG RESPONSE: CONTEXT, STRUCTURE AND FORMAT OF QUALIFICATION SUBMISSIONS

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TABLE OF CONTENTS

INTRODUCTION

1. Objective of the Guideline

The guideline describes recommendations regarding context, structure, and format of regulatory submissions for qualification of genomic biomarkers, as defined in ICH E15[1]. Biomarker qualification has not been covered in any ICH guideline. Qualification is a conclusion that the biomarker data submitted support use of the biomarker in drug discovery, development or post-approval and, where appropriate, in regulatory decision-making. The objective of the guideline is to create a harmonized structure for the qualification of genomic biomarkers that will foster consistency of applications across regions and facilitate joint discussions with and among regulatory authorities. It is also expected that the proposed document format will, where appropriate, facilitate incorporation of genomic biomarker data into specific product-related applications. Biomarker qualification can take place at any time during drug discovery, development or the post-approval period. 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 marketing authorization applications is provided in this document. The use of the CTD format would be expected when biomarker data are submitted as part of an NDA or MAA or upon request by the regulatory authorities.

2. Background

The use of biomarkers in drug discovery, development and post-approval has the potential to facilitate development of safer and more effective medicines, to guide dose selection and to enhance the benefit-risk profile of approved medicines. To support the evaluation of genomic biomarkers, a submission standard applicable across regions is described and defined within this guideline. This guideline is based on previous experiences with submissions containing genomic biomarker data in the various regions. Such submissions have been either stand alone biomarker qualification applications or a component of medicinal product-related regulatory process.

3. Scope of the Guideline

The scope of this guideline is the context, structure, and format of qualification submissions for clinical and non-clinical genomic biomarkers related to drug response including translational medicine approaches, pharmacokinetics, pharmacodynamics, efficacy and safety aspects. This guideline covers genomic biomarkers used singly or in combination with other genomic biomarkers or in combination with non-genomic biomarkers. It does not cover non-genomic biomarkers; however, it is anticipated that many of the principles described in this document might be applicable to other biomarker categories (e.g., proteomics) and other qualification contexts not associated with drug response.

This guideline does not address either the qualification process or the evidence for genomic biomarker qualification.

4. General Principles

The proposed context of use (hereinafter referred to as “context”) of a genomic biomarker should determine the data supporting its qualification. Therefore, the relevant context should be clearly detailed in the submission package. Reference should be made to the specific use of the genomic biomarker in drug development.

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, the structure

[1] ICH E15 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”.

can facilitate submission and review of future biomarker qualification submissions expanding the use of the biomarker to new contexts.
The format of the data for qualifying a genomic biomarker can vary significantly depending on the context. It is therefore only possible to provide general guidelines on data format for a genomic biomarker qualification submission. The format should support an evaluation of the genomic data and can include reports, tabulations, and raw data (if requested by regulatory authorities). Data format should be consistent with the methodology and platform used for analyzing the genomic biomarker in question. Reference to standards and/or accepted methods used should be described as applicable.
The format for a genomic biomarker submission recommended in this guideline can be applicable at any stage of drug discovery, development, or the post-approval period. The biomarker qualification submission can follow CTD format to facilitate the integration of genomic biomarker data into specific product related applications. The proposed overall organization of the biomarker qualification submission described herein corresponds to the CTD format, which consists of 5 parts (Modules 1-5). The recommended links between sections of the biomarker qualification submission and their corresponding CTD sections are as follows: ICH E16 Section 1 (Regional Administrative Information) links to CTD Module 1; Section 2 (Summaries) links to Module 2; Section 3 (Quality) links to Module 3; and Sections 4 and 5 (Non-clinical and Clinical Study Reports) link to Modules 4 and 5, respectively. More details are described in the ICH M4 and other relevant guidelines.
Applicants who wish to submit in accordance with the Electronic Common Technical Document (eCTD) format should also consult the ICH M2 guideline (Electronic Standards for Transmission of Regulatory Information) and other relevant guidelines, including regional guidelines.

STRUCTURE OF GENOMIC BIOMARKER QUALIFICATION SUBMISSIONS

The biomarker qualification submission should include the following sections:

Section 1: Regional Administrative Information[2]

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.

Section 2: Summaries [3]

Introduction

This section should be concise. It can include a description of the disease and/or experimental setting, the nature of the genomic biomarker (e.g., Single Nucleotide Polymorphisms (SNPs) and Copy Number Variation (CNV)) and provide a rationale for its use in drug discovery, development or post-approval studies.

Context[4]

The dossier structure described in this guideline is intended for genomic biomarker qualification submissions after appropriate supporting data have been generated. However, this structure can also be considered for submissions for scientific advice from regulatory authorities before or during the generation of the biomarker data intended to support qualification. The elements describing the context for a biomarker should include (i) the general area, (ii) the specific biomarker use, and (iii) the critical parameters which define when and how the biomarker should

[2] Links to CTD Module 1 (where applicable)
[3] Links to CTD Module 2 (where applicable)
[4] Links to CTD Module 2 sections 2.4 / 2.6 (nonclinical overview / summary) or 2.5 / 2.7 (clinical overview / summary) (where applicable)

be used. The context can be limited to use in drug development. It is expected that a biomarker proposed for qualification would facilitate a specific drug development program or drug use and/or would offer an improvement over currently available biomarkers and/or endpoint assessments.

The proposed context for a genomic 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 agency agrees. Important observations regarding the source of data, identified deficiencies, 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 in the overview.

Context can be described according to the following taxonomy:

- General Area (including, but not limited to)
  - Non-Clinical
    - Pharmacology
    - Safety and Toxicology
  - Clinical
    - Pharmacology
    - Safety
    - Efficacy
- Specific Biomarker Use (including, but not limited to)
  - Patient selection
    - Inclusion/Exclusion
    - Trial enrichment or stratification
  - Assessment of mechanism of action
    - Mechanism of drug 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
  - Response monitoring
    - Monitoring drug safety
    - Monitoring drug efficacy
  - Toxicity/Adverse reactions/Risk minimization
    - Indicating/predicting toxicity/adverse reactions

- Critical Parameters of Context Description (including, but not limited to)
  - Drug-specific use
  - Disease diagnosis, prognosis, or stage
  - Assay specifications
  - Tissue or physiological/pathological process addressed
  - Species
  - Demographics including ancestry and/or geographic origin
  - Environmental factors including lifestyle
  - Use in clinical trials

A biomarker could have more than one context, including the general area and/or specific use within a single submission (e.g., non-clinical and clinical predictive biomarker(s)), as shown in the following examples.

i) Non-Clinical Safety

Messenger RNA levels of kidney injury molecule 1 (*Kim-1*) and clusterin (*Clu*) can be included as genomic biomarkers of drug 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: Non-clinical safety and toxicology
- Specific Biomarker Use: assessment of mechanism of adverse reaction/toxicity and dose optimization (NOAEL in animal models)
- Critical Parameters of Context Description
    - Drug specific use: *no*
    - Assay specifications: *in vitro*
    - Tissue or physiological/pathological process addressed: *kidney*
    - Species: *Rattus norvegicus*

ii) Clinical Pharmacology/Drug Metabolism

CYP2C9 genetic variants result in poor metabolizer (PM) and extensive metabolizer phenotypes and differences in drug A exposure. Plasma levels of Drug A in patients 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 selection (inclusion/exclusion, trial enrichment or stratification), dose optimization in individual patients and toxicity/adverse reactions/risk minimization.
- Critical Parameters of Context Description
    - Drug-specific use: *Drug A*
    - Assay specifications: *Genotyping*
    - Species: *H. 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), predicted safety and mechanism of adverse reaction/toxicity.
- Critical Parameters for Context Description
    - Drug-specific use: *Drug B*
    - Assay specifications: *Genotyping*
    - Species: *H. sapiens*
    - Demographics including ancestry and/or geographic origin: *Han-Chinese*

Methodology and results [5]

This section should include a summary of nonclinical or clinical studies, including integrated analysis of the genomic biomarker qualification studies and individual study synopses.

i) Integrated analysis of the genomic biomarker qualification studies

The integrated analysis should provide a critical assessment and appraisal of overall results, including discussion and interpretation of the findings with regard to the proposed context. This section refers to the methodology and data provided in the individual study reports and other relevant information (Sections 4 and 5).

[5] Links to CTD Module 2 (where applicable)

This section should provide results across studies, using tabular representations as applicable. It should present the strengths and limitations of the biomarker qualification program and study results, analyze the benefits of the biomarker for its intended use, and describe how the study results support its use in the proposed context.
To achieve these objectives, this section can:

- Describe and explain the overall approach to the biomarker qualification program including methods and relevant aspects of study design and statistical analysis;
- Describe the rationale for the selection of population sample studied in the biomarker qualification;
- Describe the analytical performance characteristics of the assay (e.g., accuracy, precision, and other standard parameters);
- Describe the results supporting the nonclinical/clinical use of the biomarker (e.g., retrospective/prospective correlation with phenotype/outcome);
- 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);
- Provide an assessment of expected benefits 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, and how they have been evaluated and resolved;
- Identify unresolved issues, and explain why they should not be considered as barriers to qualification for the proposed context, and/or describe plans to resolve them if applicable.

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.

ii) Individual study synopses

This section is intended to 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.

Section 3: Quality[6]

Drug quality and manufacturing data would in general not be included in a biomarker qualification submission independent from an NDA or MAA.

Sections 4: (Nonclinical) and 5 (Clinical): Study Reports[7]

In this section, full study reports for biomarker qualification should be provided, and raw data could be made available to the regulatory agency upon request. Information on compliance with Good Laboratory Practices (GLP) or Good Clinical Practices (GCP) can be included in these sections. This guideline suggests that, where appropriate, the study reports can follow relevant ICH guidelines (e.g., E3, M4E, M4S) for their preparation.
Within the study reports, the appropriate format of the genomic data will depend on the characteristics of the genomic biomarker measured (e.g., SNPs, CNV) and the methodology used

[6] Links to CTD Module 3 (where applicable)
[7] Links to CTD Modules 4 and 5 for nonclinical and clinical reports (where applicable)

(e.g., microarray, Polymerase Chain Reaction). Reports should be provided using the following structure (as applicable) and should be arranged according to the following sub-headings:

- Section a
  - Assay development reports
  - Analytical assay validation reports
- Section b (as applicable)
  - Non-clinical study reports (*in-vitro*)
  - Non-clinical study reports (*in-vivo*, specify species)
- Section c (as applicable)
  - Clinical pharmacology study reports
  - Clinical efficacy and/or safety study reports

Regardless of the genomic 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 include, but need not be limited to:

- Type of sample used for genomic analysis and methods of collection, handling and storage;
- Methods used for determination of gene expression or DNA sequence and other structural characteristics;
- Criteria used for selection of candidate genes, if this is the chosen approach (candidate by position, by function, based on expression profiling data);
- Experimental data as described using, as applicable, the current internationally recognized standards;
- Methods and software used for analyses;
- Results of analyses of genomic biomarkers, including genome-wide association studies, sequencing, and molecular diagnostic assays, all of which should be described, as applicable, to current internationally recognized standards;
- Performance characteristics of the genomic biomarker test used, as based on retrospective and/or prospective correlation with non-clinical and/or clinical endpoint data as described above. These reports should include a description of the methods and study designs as well as the results of functional studies performed exploring further those genomic biomarkers identified as potentially relevant.

Copies of other documents supporting the genomic biomarker qualification submission should be provided here. 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.

ABBREVIATIONS

CNV – Copy Number Variation
CTD – Common Technical Document for the Registration of Pharmaceuticals for Human Use
DNA – Deoxyribonucleic Acid
MAA – Market Authorization Application
NDA – New Drug Application
NOAEL– No Observed Adverse Effect Level
NOEL – No Observed Effect Level
PM – Poor Metabolizer
RNA – Ribonucleic Acid
SNPs – Single Nucleotide Polymorphisms