定することが不可能となる。連結不可能匿名化の目的は、被験者が再び特定されないようにすることである。連結不可能匿名化された試料及び関連データからは被験者を特定できないため、被験者からの要求があっても試料を廃棄、または結果を本人に開示することは不可能である。連結不可能匿名化されたデータ及び試料を用いる場合、臨床モニタリングや被験者の追跡調査、被験者からの新規データの追加は不可能である。被験者の識別情報とデータや試料とを連結するコードキーの削除により、コードキーを用いて被験者を再び特定できないため、コード化されたデータ及び試料よりも機密性が高まり、被験者のプライバシーがさらに保護される。

2.3.4 非連結匿名データ及び試料（Anonymous Data and Samples）

非連結匿名データ及び試料には最初の収集段階から、個人識別情報が付与されることもなければ、コードキーが作成されることもない。従ってゲノムデータ及び試料から被験者個人が特定される可能性はない。限られた臨床データのみが非連結匿名試料と関連づけられる場合もあり得る（例：糖尿病、男性、年齢50～55、コレステロール値＞240mg/dlの被験者）。非連結匿名試料及び関連データからは被験者を特定できないため、被験者からの要求があっても試料を廃棄、または結果を本人に開示することは不可能である。非連結匿名データ及び試料を用いる場合、臨床モニタリングや被験者の追跡調査、新規データの追加は不可能である。

2.3.5 補足情報

特定のコード化分類を用いることと被験者からインフォームド・コンセントを取得することとの関係は、本ガイドラインの主旨からは外れるためここでは触れない。しかし治験関連文書（例えば、説明文書・同意文書）には、被験者へのゲノムデータ開示を含め、何らかの目的でゲノムデータと被験者の個人識別情報とを連結できるようにする場合の条件を記述するべきである。

表1：ゲノムデータ及び試料のコード化分類

試料のコード化分類		被験者の個人識別情報とゲノムバイオマーカーデータとの連結	被験者を識別できる可能性（取り得る対応例：被験者の要求に応じた試料の廃棄、被験者本人へのゲノム解析結果の開示を含む）	臨床モニタリング、被験者の追跡調査、新規データ追加の可能性	被験者の情報の機密性及びプライバシー保護の程度
識別可能 ***Identified***		（直接的に）有 被験者の特定が可能	有	有	一般的な医療上の機密性及びプライバシー保護と同程度
コード化 ***Coded***	*シングル* ***Single***	（間接的に）有 被験者の特定が可能（1つの固有なコードキーを介して）	有	有	治験の標準
	ダブル ***Double***	（非常に間接的に）有 被験者の特定が可能（2つの固有なコードキーを介して）	有	有	シングルコード化よりも高度な機密性及びプライバシー保護
連結不可能匿名化 ***Anonymised***		無 コードキーが削除されているため被験者の再特定ができない	無	無	コードキーが削除されているためゲノムデータ及び試料は被験者と連結できない
非連結匿名 ***Anonymous***		無 個人識別情報は収集されず、コードキーも作成されない 被験者の特定ができない	無	無	ゲノムデータ及び試料は一度も被験者と連結されない

Guidance for Industry

E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories

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)

April 2008
ICH

Guidance for Industry

E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories

Additional copies are available from:

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http://www.fda.gov/cder/guidance/index.htm

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http://www.fda.gov/cber/guidelines.htm.

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)

April 2008
ICH

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Contains Nonbinding Recommendations

Guidance for Industry[1]
E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories

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, 1.1, 1.3)[2]

This guidance contains definitions of key terms in the discipline of pharmacogenomics and pharmacogenetics, namely genomic biomarkers, pharmacogenomics, pharmacogenetics, and genomic data and sample coding categories. In the effort to develop harmonized approaches to drug regulation, it is important to ensure that consistent definitions of terminology are being applied across all constituents of the International Conference on Harmonisation (ICH). This guidance on definitions is intended to facilitate the integration of the discipline of pharmacogenomics and pharmacogenetics into global drug development and approval processes. As new scientific knowledge in the discipline of pharmacogenomics and pharmacogenetics emerges, the current guidance will be reviewed and expanded if appropriate.

The validation and qualification processes for genomic biomarkers, evidence for their intended use, and acceptance criteria across ICH regions are outside of the scope of this guidance.

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 Expert Working Group (Efficacy) 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, November 2007. 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, November 2007.

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

II. BACKGROUND (1.2)

Pharmacogenomics and pharmacogenetics have the potential to improve the discovery, development, and use of medicines. Each of the ICH regions has published specific pharmacogenomic and pharmacogenetic guidelines, or concept papers, and is in the process of developing others. However, the lack of consistently applied definitions for commonly used terminology raises the potential for either conflicting use of terms in regulatory documentation and guidelines or inconsistent interpretation by regulatory authorities, ethics committees, and sponsor companies.

III. GUIDANCE (2)

Definitions of a genomic biomarker, pharmacogenomics, pharmacogenetics, and genomic data and sample coding categories are detailed below. The definition of what constitutes a genomic biomarker is key to understanding the definitions of pharmacogenomics and pharmacogenetics and is therefore introduced in this guidance first. Additional information useful to an understanding of aspects covered by each of the definitions is also provided. Some of the principles described in this guidance might be applicable to proteomics, metabolomics, and other related disciplines.

A. Genomic Biomarker (2.1)

1. Definition (2.1.1)

A genomic biomarker is defined as follows:

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.

2. Additional Information (2.1.2)

a. A genomic biomarker could, for example, be a measurement of:

- The expression of a gene
- The function of a gene
- The regulation of a gene

b. A genomic biomarker can consist of one or more deoxyribonucleic acid (DNA) and/or ribonucleic acid (RNA) characteristics.

c. DNA characteristics include, but are not limited to:

- Single nucleotide polymorphisms (SNPs)
- Variability of short sequence repeats
- Haplotypes
- DNA modifications, e.g., methylation
- Deletions or insertions of (a) single nucleotide(s)
- Copy number variations
- Cytogenetic rearrangements, e.g., translocations, duplications, deletions, or inversions

d. RNA characteristics include, but are not limited to:

- RNA sequences
- RNA expression levels
- RNA processing, e.g., splicing and editing
- microRNA levels

e. The definition of a genomic biomarker is not limited to human samples, but includes samples from viruses and infectious agents as well as animal samples, i.e., for the application of genomic biomarkers to nonclinical and/or toxicological studies.

f. The definition of a genomic biomarker does not include the measurement and characterization of proteins or low molecular weight metabolites.

B. Pharmacogenomics and Pharmacogenetics (2.2)

1. Definitions (2.2.1)

a. Pharmacogenomics (2.2.1.1)

Pharmacogenomics (PGx) is defined as:

The study of variations of DNA and RNA characteristics as related to drug response.

b. Pharmacogenetics (2.2.1.2)

Pharmacogenetics (PGt) is a subset of pharmacogenomics (PGx) and is defined as:

The study of variations in DNA sequence as related to drug response.

2. Additional Information (2.2.2)

a. The term *drug* should be considered synonymous with investigational (medicinal) product, medicinal product, medicine, and pharmaceutical product (including vaccines and other biological products).

b. PGx and PGt are applicable to activities such as drug discovery, drug development, and clinical practice.

c. Drug response includes the processes of drug absorption and disposition (e.g., pharmacokinetics (PK)), and drug effects (e.g., pharmacodynamics (PD), drug efficacy, and adverse effects of drugs).

d. The definitions of PGx and PGt do not include other disciplines such as proteomics and metabolomics.

C. Categories for Genomic Data and Samples Coding (2.3)

PGx and PGt research depends on the use of biological samples to generate data. A harmonized definition for the coding of these samples and their associated data will facilitate use in research and development of new medicines.

There are four general categories of coding: identified, coded, anonymized, and anonymous. Coded data or samples can be single or double coded.

The implications of using a specific data and sample coding category should be considered in the design of PGx and PGt research studies.

Some implications are highlighted in this section and summarized in Table 1.

1. Identified Data and Samples (2.3.1)

Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). As the samples and associated data are directly traceable back to the subject, it is possible to undertake actions such as sample withdrawal or the return of individual results in accordance with the subject's request. The use of identified data and samples allows for clinical monitoring, subject follow-up, and the addition of new data from the subject. Identified data and samples offer privacy protection comparable to that of general health care confidentiality in everyday medical practice. Identified data and samples are generally not considered appropriate for purposes of clinical trials in drug development.

2. Coded Data and Samples (2.3.2)

Coded data and samples are labeled with at least one specific code and do not carry any personal identifiers.

a. Single-Coded Data and Samples (2.3.2.1)

Single-coded data and samples are usually labeled with a single specific code and do not carry any personal identifiers. It is possible to trace the data or samples back to a given individual with the use of a single coding key. In general, the clinical investigator is responsible for maintaining the coding key. As the samples and associated data are indirectly traceable back to the subject via the coding key, it is possible to undertake actions such as sample withdrawal or the return of individual results in accordance with the subject's request. The use of single-coded data and samples allows for clinical monitoring, subject follow-up, or the addition of new data from the subject. Single coding is the current standard used in clinical research and offers additional safeguards to the subject's identifiers compared to the general health care confidentiality and privacy protection in everyday medical practice.

b. Double-Coded Data and Samples (2.3.2.2)

Double-coded data and samples are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. In general, the clinical investigator is responsible for maintaining the first coding key and does not have access to the second coding key. As the samples and associated data can very indirectly be traced back to the subject via the use of both coding keys, it may be possible to undertake actions such as sample withdrawal, or the return of individual results in accordance with the subject's request. However, additional electronic or technical processes may be added to further limit the ability to trace back from a genotype result to an individual subject (for example, a specific computer process that allows new subject data to be added but prevents the reconnection of the genotype data back to the individual subject identifier). The use of double-coded data and samples allows for clinical monitoring, subject follow-up, or the addition of new data from the subject. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both coding keys is needed to link any data or samples back to a subject identifier.

3. Anonymized Data and Samples (2.3.3)

Anonymized data and samples are initially single or double coded but where the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification. As anonymized samples and associated data are not traceable back to the subject, it is not possible to undertake actions such as sample withdrawal, or the return of individual results, even at the subject's request. The use of anonymized data and samples does not allow for clinical monitoring, subject follow-up, or the addition of new data from the subject. The deletion of the coding key(s) linking the data and samples to a given subject's identifiers provides additional confidentiality and privacy protection over coded data and samples, as it prevents subject re-identification through the use of the coding key(s).

4. Anonymous Data and Samples (2.3.4)

Anonymous data and samples are never labeled with personal identifiers when originally collected, neither is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. In some instances, only limited clinical data can be associated with anonymous samples (e.g., samples from subjects with diabetes, male, age 50-55, cholesterol>240 mg/dl). As anonymous samples and associated data are not traceable back to subjects, it is not possible to undertake actions such as sample withdrawal, or the return of individual results, even at the subject's request. The use of anonymous data and samples does not allow for clinical monitoring, subject follow-up, or the addition of new data.

5. Additional Information (2.3.5)

The use of a specific coding category in relation to obtaining informed consent from subjects is not within the focus of this guidance and is not addressed in this guidance.

The conditions under which the genomic data can be linked back to a subject's personal identifiers for any purpose, including the return of genomic data to the subject, should be described in research related documents, e.g., the informed consent document.

Table 1: Summary of Genomic Data and Sample Coding Categories

Sample Coding Category		Link Between Subject's Personal Identifiers And Genomic Biomarker Data	Traceability Back to the Subject (Actions possible, including e.g., sample withdrawal or return of individual genomic results at subject's request)	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (direct) Allows for subjects to be identified	Yes	Yes	Similar to general health care confidentiality and privacy
Coded	***Single***	Yes (indirectly) Allows for subjects to be identified (via single, specific coding key)	Yes	Yes	Standard for clinical research
	Double	Yes (very indirectly) Allows for subjects to be identified (via the two specific coding keys)	Yes	Yes	Added privacy and confidentiality protection over single code
Anonymized		No Does not allow for subjects to be re-identified as coding key(s) have been deleted	No	No	Genomic data and samples no longer linked to subject as coding key(s) have been deleted
Anonymous		No Identifiers never collected and coding keys never applied Does not allow for subjects to be identified	No	No	Genomic data and samples never linked to subject

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

GENOMIC BIOMARKERS RELATED TO DRUG RESPONSE: CONTEXT, STRUCTURE AND FORMAT OF QUALIFICATION SUBMISSIONS

E16

Current *Step 2* version

dated 10 June 2009

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

E16
Document History

Current *Step 2* version

Code	History	Date
E16	Approval by the Steering Committee under *Step 2* and release for public consultation.	10 June 2009

GENOMIC BIOMARKERS RELATED TO DRUG RESPONSE: CONTEXT, STRUCTURE AND FORMAT OF QUALIFICATION SUBMISSIONS

E16

Draft ICH Consensus Guideline

Released for Consultation on 10 June 2009, at *Step 2* of the ICH Process

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GENOMIC BIOMARKERS RELATED TO DRUG RESPONSE: CONTEXT, STRUCTURE AND FORMAT OF QUALIFICATION SUBMISSIONS

E16

1. INTRODUCTION

1.1 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.

1.2 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.

1.3 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

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[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".

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.

1.4 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 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.

2. 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 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

[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 (non-clinical overview/summary) or 2.5/2.7 (clinical overview/summary) (where applicable)

        - 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 non-clinical or clinical studies, including integrated analysis of the genomic biomarker qualification studies and individual study synopses.

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