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# 4 Reflection paper on co-development of pharmacogenomic 5 biomarkers and Assays in the context of drug 6 development

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# Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development

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# 1. Introduction (background)

The increasing knowledge of variation within the human genome is being used for the development of personalised and stratified medicine, with the aims of decreasing the number of adverse drug reactions and increasing the efficacy of drug therapy. Significant pharmacogenomic research has focused on understanding the molecular mechanisms underlying certain adverse drug reactions and on recognising biomarkers (BMs) that identify individuals at risk.

A genomic biomarker (in this document referred to as PGBM) is 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[1].

The co-development of drugs and PGBMs may open new and often contentious issues: they need to be addressed in the different contexts of PGBM use, moving progressively from PGBM discovery to PGBM use in non-clinical phases and finally to clinical phases of drug development.

An individual assay implies a specific test method, reagents and platform which are developed and validated together for the detection, choice and measurement of specific PGBMs. The assay may be subject to performance evaluation during a qualification process independently of a specific drug under development consideration. The level of scientific stringency applied to the assay will depend on the knowledge accumulated about the PGBM and the drug(s) under consideration, as well as the implication of its use.

It is recognised that for well established PGBMs relevant to drug developments such as the CYP 450 polymorphic enzymes, there are commercially available *in vitro* diagnostic medical devices (IVDs).

However, for discovery PGBMs, when initially used specifically in non-clinical toxicity or pharmacology studies, and planned to be used afterwards in the clinical drug development context, either customization of existing assays or new development of specific tests may be needed (e.g. assays to identify PGBMs based on new splicing iso-forms or new mRNA profiles).

# 2. Scope and objective of this paper

The scope of this paper is the co-development of a new PGBM and the relevant assay(s) in the context of either a drug development or for qualification purposes[2].

The scope includes PGBMs in the context of assessing drug-response (toxicity, PK/PD, dose-response, efficacy or adverse reactions), condition/disease and PGBM used for optimizing clinical trials design.

The Qualification procedure for biomarkers development shall be considered in order to obtain scientific advice on Biomarker assays co-development (see EMA webpage http://www.ema.europa.eu/pdfs/human/biomarkers/7289408en.pdf).

This paper intends to support the qualification of PGBM, reflecting on the key scientific principles that need to be met in order to ensure that the performance of the chosen PGBM assay is sufficiently reliable for the further use of the PGBM to optimise drug development and regulatory submission.

It will address issues related to timing of test and drug co-development; therefore some scenarios will be drafted taking on board both PGBM assays and product development. The principles described under each scenario may be relevant for PGBM qualification purposes.

Whilst this paper focuses on co-development of genomic biomarkers and assays, some principles may be applicable to co-development of other types of BMs.

The legal requirements for IVDs or other medical devices are outside the scope of this paper and are addressed in other relevant legislation and guidelines[3] .

[1] http://www.ema.europa.eu/pdfs/human/ich/43798606en.pdf
[2] http://www.ema.europa.eu/pdfs/human/biomarkers/7289408en.pdf

# 3. Critical parameters for the choice of Biomarker assay

The intended use[4] of the PGBM should be thought through before development and validation of the chosen assay.

When developing the prototype assay for a PGBM, it is crucial that the selection of the specific form of the chosen PGBM to be measured is carefully considered and justified (this is particularly relevant for polymorphic PGBMs as it is the case for the different splicing iso-forms of genetic variants).

At the stage of early testing of the PGBM for drug development, appropriate key standards and controls should be selected which are suitable to be carried forwards during the entire assay development (e.g. house-keeping genes for mRNA profiling, working standards for the analyte).

Internationally recognized standard materials, if available, should be included in the characterization of the assay at early stage.

***Assay-specific considerations***

These include, known attributes of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, linear range of quantitative assays, including control of known relevant interference, and limits of detection5. Analytical performance criteria should be defined and justified in a pragmatic way so as to be proportionate to the stage of development and to risks and benefits of its intended use ("fit-for-purpose").

***Pre-analytical factors***

- General principles of specimen acquisition regarding PGx markers (e.g. dynamic vs. static PGx markers).
- Sample type (including any matrix factors).
- Patient or subject selection criteria, conditions and preparation for sampling.
- Sample handling, e.g. storage conditions, extraction procedure.

***Analytical factors:***

- Assay protocol.
- Assay platform including amplification efficiency, linearity, precision, dynamic range as well as limit of detection.
- Calibrators and QC.
- Software and algorithms used for the interpretation of results.
- Performance variables.

***Post analytical factors:***

- Data handling and processing[6].
- Relevant published data, meta-data and standards available.
- Comparative performance with relevant standard if available or state-of-the art test.

***Validation steps in the development of an assay for a pharmacogenomic biomarker:***

- Assay performance evaluation:
  - Validation of analytical performance (e.g. detection of the biomarker[7]).
  - Validation of in vivo clinical performance as relevant for context and intended uses (i.e. sensitivity and specificity in detecting clinically relevant response or status, appropriate cut-off level for ROC interpretation etc.).
  - Further plans in post market surveillance to confirm clinical utility.

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[3] See in particular Directive 98/79/EC, as amended on in vitro diagnostic medical devices http://ec.europa.eu/enterprise/sectors/medical-devices/regulatory-framework/index_en.htm

[4] Reference to the ICH E16 to explain what intended use means in this context: http://www.ema.europa.eu/pdfs/human/ich/38063609endraft.pdf

5 [DN – quoted from the IVD Directive 98/79/EC – annex 1 para A3])

6 http://www.ema.europa.eu/pdfs/human/pharmacogenetics/53620107en.pdf

7 ISO standard

# 4. Scenarios for PGBM and drug co-development

PGBM measurement can be assessed at different biological levels with different technologies; thus, the appropriate choice of assay depends both on the application of the PGBM and the features and limitations of the respective technology. Various types of assays can be used in the PGBM discovery process and these range from the relatively "low technology" end, such as immuno-histo-chemistry to immunoassays, to the "high technology" end, including genomic, proteomic, and multiplex ligand-binding assays. Integration of various technologies is proving pivotal not only for PGBM identification and characterisation but also for validation. In fact, an assay applied in biomarker discovery can also be further developed and used as an analytical assay in the clinical setting. In all cases crucial element to be considered is the choice of positive and negative controls to ensure reliability of the measurements.

The co-development of the PGBM/assay and a drug should be seen as a continuous process that goes through analytical validity of the PGBM assay at early stage of the drug development, clinical validity / studies of PGBM (to ensure that the PGBM assay is able to select/stratify patients) and ultimately clinical usefulness (ability of the PGBM test to ensure that the patient selected will have an improved benefit-risk profile when treated with the drug after PGBM testing in addition to conventional clinical features). The approach taken in this document is an ideal scenario to discuss key points applicable to various stages of drug/biomarker co-development, whilst it is acknowledged that biomarker discovery may occur at any stage of drug development prior as well as after initial marketing authorization is granted for the medicinal product.

During the co-development of the drug and of the PGBM assay the use of a central laboratory facilities is the preferred option in order to ensure consistency in the results observed. Quality assurance networks of clinical laboratories shall be encouraged to obtain evidence of reproducibility in the validation steps of the PGBM assy.

### *(4.1) Discovery biomarkers and assays*

It is important that the development of the PGBM assay is initiated early in the drug development process to be able to bridge data obtained later during clinical PGBM qualification.

A prototype assay might be acceptable for in vitro and non-clinical drug development studies, but should have the essential characteristics permitting its evaluation: acceptable methods/assays, tissue and disease specificities. Parameters associated with sensitivity and specificity of the biomarker shall be proportionate to supporting the rationale for the non-clinical and clinical applications of the BM, and according to the development phase precision, accuracy, reproducibility, detection levels justified for the intended use.

The prototype of the assay could also rely on simplified procedures – it could be intuitive and easy-to-use, with dynamic visualization, lowered consumption of samples, reagents and energy - to keep up with standard analytical capabilities. Therefore the assay should have a flexible design environment for intuitive layout.

Moreover, for future clinical utilization of the platform chosen, appropriate plans are also required at the stage of prototype assay development for an efficient control of instruments and the ability to generate sufficient and appropriate data to validate the assay, to facilitate incorporation of quality assurance and control measures and, as appropriate, to meet the legal requirements for IVDs[3].

### *(4.2) Translational PGBM*

During drug development, when an assay is used to confirm that the findings from in vitro and animal studies (or the initial observation about the behavior of the PGBM e.g. possible safety marker identified on preclinical data,) are relevant to the human in vivo context.

The pre-requisite of a translational BM is therefore that

- the same entity is identified and measured both in animal and man and that
- the functionality associated to the BM is consistent in the two species

Therefore the PGBM assay needs to be consistent enough to support the extrapolation of PGBM effects observed in animal studies in humans, among a complex set of variables and situations. (see Doc. Ref.EMEA/CHMP/SWP/28367/07).

It should be demonstrated that the assay identifies the same BM as in animal studies; the analytical performance characteristics of the assay, such as the limit of detection appropriate for the intended use, accuracy, and repeatability need to be confirmed at this stage. There might be the situation that the assay of animal studies has to be adapted to the human situation to cope with respective differences, e.g. the nucleic acid sequence differences of the gene of interest.

Basic performance data need to be generated addressing comparative assay performance in clinical vs. preclinical specimens.

Limited QA/QC data based on exploratory use of PGBM may be considered acceptable on a case-by-case basis, depending on the intended use of the BM.

### *(4.3) Clinical - stage PGBM*

General principles on evidentiary standards related to clinical PGBM qualification (e.g. PGBM used for subject selection or stratification in phase II- IIb clinical trial) include

- Stability of the PGBMs over time and in relation to different phases/status of the clinical phenotype
- Biological rationale and preliminary data to especially differentiate (disease) prognostic PGBM from predictive PGBM (drug response)
- Performance of the PGBM in predicting response/outcome
- Performance of the test in predicting response/outcome
- More extensive data on analytical performance of the assay;

All aspects of PGBM use should be GCP-compliant especially if the PGBM is intended to be used in a clinical context for the purpose of patients selection as:

- Diagnostic
- Prognostic
- Predictor of dose-exposure
- Predictor of drug response (safety, efficacy)

### *(4.4) PGBM for patient selection in confirmatory clinical trials as part of a MAA and of Risk Management Plans ("Companion diagnostic")*

Methodological issues associated to the use of PGBM in confirmatory clinical trials are addressed in other CHMP guidelines/reflection papers.

All processes related to sample and data handling and assay methodology are to be done in compliance with GLP and GCP standards and current guidelines as applicable.

At this stage of clinical development it should be ensured that the candidate companion diagnostic used in clinical trials is suitable for clinical validation and clinical usefulness (e.g. determination of the cut-off, determination of threshold values for quantitative assays). Full documentation of all aspects of analytical performance shall be available at this point of the biomarker assay development and of the drug development, to prepare for and facilitate the transition of the testing methodology in the post-approval clinical use.

As appropriate demonstration of performance versus existing reference tests may be provided (e.g. retrospective evaluation of original specimens in completed studies with known outcome).

At the time of evaluation of the main trials results, sufficient evidence shall be available to allow description in the EPAR and in the SPC (when appropriate) of the main characteristics of the assay used in clinical development.

After approval of the pharmaceutical to be used with a companion PGBM diagnostic, when appropriate the post market surveillance activities may include:

- Demonstration or confirmation of consistency of results obtained with the advanced PGBM assay used in pivotal clinical trials (e.g. research-grade) and with the assay implemented post-approval, be it a commercial kit or a test performed in accredited clinical laboratories.
- Review of literature relevant to the chosen biomarker and associated assays.

If an alternative test platform/technology is further developed for an assay to be used in conjunction with a specific medicinal product for which the test is recommended e.g. for dose adjustment, for selection or exclusion of patients to treatment, ascertainment of the consistency of the results obtained with the two assays (the one already evaluated based on clinical trial(s) data and the new one intended for the clinical use) is recommended.

# References


- Position paper on terminology in Pharmacogenetics (EMEA/CPMP/3070/01)
- Reflection paper on pharmacogenomic samples, testing and data handling (EMEA/CHMP/201914)
- ICH Topic E 15: Establish definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories (CHMP/ICH/437986/2006)
- Reflection paper on the use of pharmacogenetic in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/641298/2008)
- Qualification of novel methodologies for drug development: guidance to applicants (EMEA/CHMP/SAWP/72894/2008)
- ICH Topic E 16: Note for guidance on genomic biomarkers related to drug response: context, structure and format of qualification submissions
- ISO 13612:2002 Performance evaluation of in vitro diagnostic medical devices


# Abbreviations

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| EMEA | European Medicines Agency |
| EWP | Efficacy Working party |
| FISH | Fluorescent in Situ hybridisation technique |
| ICH | International Committee for Harmonisation |
| mRNA | messenger RNA |
| PCRs | Polymerase chain reactions |
| PGt | Pharmacogenetics |
| PGx | Pharmacogenomics |
| RNA | Riboneucleic acid |
| RT-PCR | Reverse transcriptase- PCR |
| SNP | Single nucleotide polymorphism |
| SmPC | Summary of Product Characteristics |
| MAA | Marketing Authorization Application |
| SmPC | Summary of Product Characteristics |
| GPC | Good clinical Practice |