



COMMITTEE FOR HUMAN MEDICINAL PRODUCTS

**GUIDELINE ON
PHARMACOGENETICS BRIEFING MEETINGS**

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EXECUTIVE SUMMARY

Early in 2003, the CHMP released a Concept Paper on "Briefing Meetings on Pharmacogenetics"¹ to facilitate an informal process of sharing scientific and technical information between applicants and regulators. The CHMP set up the Pharmacogenetics Working Party to assist on scientific discussions relevant to the implementation of Pharmacogenetics in medicines development and the impact on regulatory assessment. This guideline is intended to provide guidance to the applicants on when and how to prepare for such dialogue with the Pharmacogenetics Working Party of the CHMP, and provides initial considerations on the format of submissions of pharmacogenetic data in informal regulatory submissions.

1. INTRODUCTION (background)

The pharmacogenetics knowledge base is still at an early stage and therefore little is known about data analysis, interpretation and evaluation of the clinical relevance of data gathered so far.

The objective of the briefing meetings is to allow applicants and the Pharmacogenetics Working party to share and discuss in an informal setting the technical, scientific and regulatory issues that arise by the inclusion of pharmacogenetics and pharmacogenomics in the development strategy and to assess their potential implications in the regulatory processes.

The Pharmacogenetics working party is multidisciplinary in its composition and includes independent experts in medicines evaluation as well as experts in the diverse scientific, ethical and regulatory matters relevant to the new genomic technologies in medicinal products development and assessment.

The composition of the Pharmacogenetics Working Party ensures further reflection on the issues discussed in the briefing meetings at the CHMP level, the Efficacy Working Party, the Scientific Advice Working Party and other related bodies of the EMEA.

Via the briefing meetings the Working Party gets input from applicants on the circumstances and rationale under which pharmacogenetic data is generated. During the meetings, regulators and academia experts may identify and discuss informally with the Applicants on issues that could create concerns at a later stage of development or in formal regulatory procedures and make alternative proposals. Therefore these dialogues may contribute to minimizing the risks of creating inadvertent obstacles to the use of this novel technology.

The applicants on the other hand have the opportunity to gain input from the CHMP expert group in an informal setting, i.e. without regulatory impact on the products under development as the experts will not engage in formal pre-assessment of the information provided for the briefing meeting. However, issues identified and questions debated during the briefing meetings constitute useful information assets intended for preparing both product specific procedures – such as scientific advice and marketing authorisation applications - and future guidance.

2. SCOPE

This guideline addresses:

- Description of the organizational steps to plan a briefing meeting
- Format and content of the background scientific information
- Outcome of the meeting

¹ (CHMP/4445/03) issued on 23rd January 2003

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) of the Annex I to Directive 2001/83 as amended.

4. DESCRIPTION OF THE STEPS TO PLAN A BRIEFING MEETING

4.1 Timelines for action when requesting a briefing meeting

The briefing meeting may take place at any time at request of the applicant

- i. when new pharmacogenetic information becomes available during the development of a medicinal product (pre- or post-authorisation)

or

- ii. when the applicant wishes to explore a new indication for an approved product based on recent developments in pharmacogenetics

The briefing meetings are linked to the plenary meetings of the CHMP Pharmacogenetics Working Party. The dates for the meetings are announced annually within the working program of the working party.

In order to prepare the meeting, the EMEA secretariat should receive the request from the Applicant together with the following information in abbreviated format at least eight weeks in advance:

- Proposed agenda for the meeting with an overview of key issues and questions for discussion, including
 - i. Specification of the area (therapeutic field or other aspects) to which the case study belongs
 - ii. Identification of main issues for discussion (in order for the EMEA to ensure participation of the necessary experts)

Four weeks before the meeting the applicant shall provide, via secure transmission (such as Eudralink)² the following information

- Briefing document (this is the Background Scientific information the applicant provides to the secretariat in preparation of the meeting)
- Preliminary list of participants (incl. their relevant expertise)

Upon receipt of the information from the Applicants, the EMEA secretariat in conjunction with the Chairman of the working party will appoint the PGWP coordinator and review the documentation in order to decide whether additional expertise is required for the briefing meeting.

In addition, the applicant shall at that time be informed of the overall meeting duration and the formal presentation can be tailored accordingly (a maximum of 60 minutes).

One week before the meeting the coordinator will circulate an initial review of the documentation submitted to the PGWP for comments.

The Members of the Working Party as well as observers and all experts are bound and shall be bound, even after the cessation of their duties, not to disclose any information, which, by its nature, must be covered by individual professional secrecy.

Two working days before the meeting, the applicant shall provide the following information:

² ² On request the EMEA will arrange Eudralink accounts for secure transmission of confidential information

- If a presentation is to be made, a copy of the presentation should be provided on CD-Rom or via secure transmission (such as Eudralink)
- Final list of participants (applicant & their experts)

4.2 Conduct of the meeting

The briefing meetings are optional and not mandatory. Participation in the voluntary briefing meetings would be advisable for future applicants if studies were being undertaken with a view to the generation of pharmacogenetic and pharmacogenomic relevant biomarkers that would result in patient selection, dose selection, treatment outcome prediction or if advice was being sought for any other reason related to pharmacogenomics.

All participants (Working Party members and experts as well as applicants' experts) at these briefing meetings are bound by standard EMEA confidentiality agreements

The outline of the meeting may include:

- Presentation by Applicant and identification of key issues (30 – 60 minutes).
- Discussion of options/issues identified with the working party experts
- Closure of meeting

The duration of the briefing meeting depends on the subjects raised by the applicants. Generally, any presentation by the applicant should not be longer than 30-60 minutes. A working party of applicants' experts (5 at maximum) would participate. Use of tele- and video-conferencing would be made available to facilitate participation of additional relevant expertise both from the applicants and regulators sides.

4.3 Outcome from the meeting

A confidential short summary of the case study and of the key issues discussed will form a dedicated section in the Pharmacogenetic expert working party's minutes to the CHMP

One week after the meeting the Company should provide a brief summary of the results of the discussion with the PGWP. This summary will be reviewed by the EMEA secretariat together with the Chairman and the PGWP coordinator and will form the basis of the final summary of the briefing meeting, which will be sent to the applicant in four weeks time after receipt of their summary.

It is strongly recommended that the applicant includes the summary of the briefing meetings in any subsequent dossier.

5. FORMATS AND CONTENT OF THE BACKGROUND SCIENTIFIC INFORMATION (BRIEFING DOCUMENT)

Prior to the meeting with the CHMP PGWP working party, the applicants should provide sufficient information to allow for an informed discussion with the working party.

For very early phase programs, only very preliminary clinical results may be available. In such situations the discussions could be conducted based on the available data at the time and the expected results in order to obtain very early input and questions from the experts.

The information should be sufficient to define the rationale of the company for pursuing the exploration of the pharmacogenetics or pharmacogenetic biomarker during the development of the product.

Exploratory data resulting from those studies, which may have an impact on development strategy choice, can be submitted in the form of summaries and synopsis in preparation of the briefing meeting. New statistical approaches could be described in the form of narrative summaries. Investigators' brochures outline could also represent a suitable format. References to published methodological articles, if available, should be provided.

The applicant should provide a description of the type of studies and protocols that have included or will include pharmacogenetics data collection be those in relation or not with specific medicinal product(s) development.

The approaches to identifying and investigating a biomarker could be either genome-wide scan or candidate gene approach. When a candidate gene approach is undertaken, the information (or Briefing document) should also include the rationale for the choice of the pharmacogenomic biomarkers selected in the study presented, a description of the methodology for the DNA sequencing and genotyping or expression profiles analyses, the available results and any additional information that will allow the experts to interpret the findings.

For the purpose of this document, a biomarker is defined in accordance with the definition proposed by the NIH Definition Working Group³. The Applicant shall justify the use of the biomarker as a tool for focussing the development programme, and as relevant discuss the robustness of the marker with respect to the potential impact on benefit risk evaluations describing the relationship of the PG biomarker with the disease, with the medicinal product response, in the specific clinical context.

5.1 Experimental design of the pre-clinical and clinical studies identified for discussion

The following information may be provided:

1. Chosen design and rationale
2. The population selected for PG studies (species, age, gender and other variables related to the phenotype e.g. for human exposure, ethnic group):
 - in the target population or relevant animal model
 - in the study population, e.g. matched groups (responders/non responders; presence/absence of adverse events...)
3. The population size selected for PG studies and a discussion on the power to detect an association, if appropriate
4. Predictive values (positive and negative) of the PG biomarkers as per clinical trials experience
5. Assumptions on clinical utility (e.g. benefit in using predictive pharmacogenetics testing versus other predictive biomarkers, use of a pharmacogenetic biomarker as a segregation marker or as a stratification tool for a subpopulation in a general matching population).

5.2 Statistical methodology

- The hypothesis to be tested shall be described and justified
- Statistical tests, models and underlying assumptions
- A description of the techniques used to avoid bias in association studies (i.e. tests for population stratification, including the use of neutral-unlinked genetic markers)
- Correction for multiple testing.
- A description of the variables included in the statistical analysis
- A description of the software used for data management and statistical analysis
- Simulated data may be used when the discussion is about issues on methodology and tests of validity

5.3 Pharmacogenetic testing methodology

³ A biomarker is “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathologic processes or pharmacologic responses to a therapeutic intervention.”

The following aspects relevant to the pharmacogenetic testing methodology chosen shall be concisely reported in the format usually required for a scientific publication or as a summary document including short annexes, along the lines of an investigator brochure.

1. For pharmacogenetic biomarkers defined via expression profile studies:
 - a summary of standardized report on gene expression microarray experiment using the MIAME (Minimum Information About a Microarray Experiment) format (see MIAME Check list in Annex I or consult the web page: <http://www.mged.org/workgroups/miame.html>);
 - Description of the methods used for selection and validation of gene expression profile of interest
 - Possible links with other established techniques (e.g. HIA)
2. For pharmacogenetic biomarkers defined via DNA sequencing and DNA variants analysis:
 - Description of the criteria used for identification of candidate genes, if this is the chosen approach, (candidate for position, for function, expression profile....)
 - Description of the method(s) used for DNA sequencing, SNPs identifications and screening.
 - Description of method(s) used for genome-wide analysis.
 - Description of the method(s) used for haplotypes determination.

The applicant shall also provide as relevant, in summarised format, the following information:

- A description of specificity and sensitivity of the test used for the association study
- A description of functional studies conducted for associated SNPs/haplotypes (in support of biological plausibility, or to discover new functions)
- Impact on clinically relevant phenotype

5.4 Genetic epidemiology of the trait identified for discussion

Following descriptions should be provided:

- Frequencies of the genetic marker in the general population (including Hardy-Weinberg equilibrium test)
- Predictive value (positive and negative) for the chosen biological or clinical outcome
- Frequencies of the genetic marker in other ethnic groups (if known and relevant)

DEFINITIONS⁴

Pharmacogenetics

Is the study of interindividual variations in DNA sequence related to drug response.

Pharmacogenomics

Is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development

Allele

⁴ Sources: CHMP position paper on terminology in pharmacogenetics (EMEA/CPMP/3070/01); Human Genome Project glossary

Alternative form of a genetic locus; a single allele for each locus is inherited from each parent (e.g., at a locus for eye colour the allele might result in blue or brown eyes).

Exon

The protein-coding DNA sequence of a gene.

Gene

The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e., a protein or RNA molecule).

Genetic polymorphism

Difference in DNA sequence among individuals, groups, or populations (e.g., genes for blue eyes versus brown eyes).

Gene expression

The process by which a gene's coded information is converted into the structures present and operating in the cell. Expressed genes include those that are transcribed into mRNA and then translated into protein and those that are transcribed into RNA but not translated into protein (e.g., transfer and ribosomal RNAs).

Gene chip technology

Development of cDNA microarrays from a large number of genes. Used to monitor and measure changes in gene expression for each gene represented on the chip.

Gene mapping

Determination of the relative positions of genes on a DNA molecule (chromosome or plasmid) and of the distance, in linkage units or physical units, between them.

Genome

All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genomics

The study of genes and their function.

Haplotype

A way of denoting the collective genotype of a number of closely linked loci on a chromosome.

High-throughput sequencing

A fast method of determining the order of bases in DNA.

Intron

DNA sequence that interrupts the protein-coding sequence of a gene; an intron is transcribed into RNA but is cut out of the message before it is translated into protein.

See also: exon

Junk DNA

Stretches of DNA that do not code for genes; most of the genome consists of so-called junk DNA which may have regulatory and other functions. Also called non-coding DNA.

Locus (pl. loci)

The position on a chromosome of a gene or other chromosome marker; also, the DNA at that position. The use of locus is sometimes restricted to mean expressed DNA regions.

Microarray

Sets of miniaturized chemical reaction areas that may also be used to test DNA fragments, antibodies, or proteins.

Directed sequencing

Successively sequencing DNA from adjacent stretches of chromosome.

Polymorphism

Difference in DNA sequence among individuals that may underlie differences in health. Genetic variations occurring in more than 1% of a population would be considered useful polymorphisms for genetic linkage analysis.

Population genetics

The study of variation in genes among a group of individuals.

Regulatory region or sequence

A DNA base sequence that controls gene expression.

Single nucleotide polymorphism (SNP)

DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered.

Transcription

The synthesis of an RNA copy from a sequence of DNA (a gene); the first step in gene expression.

REFERENCES (scientific and / or legal)

[1] A. Brazma, P Hingamp, J Quackenbush, et al. Minimum information about a microarray experiment (MIAME)—toward standards for microarray data, *Nature Genetics*, Vol 29 (2001), 365-371.

Note: See <http://publications.eu.int/code/en/en-250304.htm> for guidance on referencing published information and <http://publications.eu.int/code/en/en-130102.htm> for guidance on referencing EU texts. References to related guidelines should also be included.

Experiment Design:

- Type of experiment: for example, is it a comparison of normal vs. diseased tissue, a time course, or is it designed to study the effects of a gene knockout?
- Experimental factors: the parameters or conditions tested, such as time, dose, or genetic variation.
- The number of hybridizations performed in the experiment.
- The type of reference used for the hybridizations, if any.
- Hybridization design: if applicable, a description of the comparisons made in each hybridization, whether to a standard reference sample, or between experimental samples. An accompanying diagram or table may be useful.
- Quality control steps taken: for example, replicates or dye swaps.
- URL of any supplemental websites or database accession numbers

Samples used, extract preparation and labelling:

- The origin of the biological sample (for instance, name of the organism, the provider of the sample) and its characteristics: for example, gender, age, developmental stage, strain, or disease state.
- Manipulation of biological samples and protocols used: for example, growth conditions, treatments, and separation techniques.
- Protocol for preparing the hybridization extract: for example, the RNA or DNA extraction and purification protocol.
- Labelling protocol(s).
- External controls (spikes).

Hybridization procedures and parameters:

- The protocol and conditions used during hybridization, blocking and washing.

Measurement data and specifications:

- The quantisation based on the images.
- The set of quantisation from several arrays upon which the authors base their conclusions. While access to images of raw data is not required (although its value is unquestionable), authors should make every effort to provide the following:
 - Type of scanning hardware and software used: this information is appropriate for a materials and methods section.
 - Type of image analysis software used: specifications should be stated in the materials and methods.
 - A description of the measurements produced by the image-analysis software and a description of which measurements were used in the analysis.
 - The complete output of the image analysis *before* data selection and transformation (spot quantisation matrices).
 - Data selection and transformation procedures.
 - Final gene expression data table(s) used by the authors to make their conclusions *after* data selection and transformation (gene expression data matrices).

Array Design:

- General array design, including the platform type (whether the array is a spotted glass array, an in situ synthesized array, etc.); surface and coating specifications (when known – often commercial suppliers do not provide this data); and the availability of the array (the name or

make of commercially available arrays).

- For each feature (spot) on the array, its location on the array and the ID of its respective reporter (molecule present on each spot) should be given.
- For each reporter, its type (e.g., cDNA or oligonucleotide) should be given, along with information that characterizes the reporter molecule unambiguously, in the form of appropriate database reference(s) and sequence (if available).
- For commercial arrays: a reference to the manufacturer should be provided, including a catalogue number and references to the manufacturer's website if available.
- For non-commercial arrays, the following details should be provided:
 - The source of the reporter molecules: for example, the cDNA or oligo collection used, with references.
 - The method of reporter preparation.
 - The spotting protocols used, including the array substrate, the spotting buffer, and any post-printing processing, including cross-linking.
 - Any additional treatment performed prior to hybridization.