



European Medicines Agency

London, April 2008
Doc. Ref. EMEA/CHMP/PGxWP/128435/2006

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS

REFLECTION PAPER ON PHARMACOGENOMICS IN ONCOLOGY

DRAFT AGREED BY THE PG WORKING PARTY	April 2008
ADOPTION BY CHMP [FOR RELEASE FOR CONSULTATION]	April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	July 2008

Comments should be provided electronically in word version to lana.christiansen@emea.europa.eu

KEYWORDS	<i>Pharmacogenetics, pharmacogenomics, oncology, polymorphisms, metabolism enzymes, receptors</i>
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1. BACKGROUND

The last decade has seen rapid progress and development in the understanding of genetic influences that underlie inter-individual differences in drug action and drug response. This includes areas of pharmacogenomics that study genetic variability in relation to drug transport, drug product metabolism, enzymes responsible for metabolism, and drug response. All these aspects may have genetic determinants or markers. The objectives of such exploration has been to identify subset of individuals notable by a common marker or characteristic that may determine either increased efficacy or increased risk of adverse events, i.e., improved risk benefit analysis. Such explorations and studies have included variety of products and clinical areas such as Oncology.

The need for a paper that examined the impact of pharmacogenomic/pharmacogenetic PG information on the regulatory process in oncology was felt by the working group, the CHMP and the industry in general. The purpose of such a reflection paper would be to examine the data available so far in this 'up and coming' field with a view to providing guidance towards regulatory data requirements regarding PG information in the field of oncology with emphasis on the information to be included in the product literature such as the SPC.

This reflection paper examines the impact of PG on the European (EMA) regulatory experience in oncology wherein such pharmacogenomic information has been available in the clinical trials, in defining improved risk benefit analysis of a particular product and how such information has influenced authorisation of these products, in addition to examining methods of conveying this in the product information.

This reflection paper should be read in conjunction with the following notes for guidance:

- Pharmacokinetic studies in man (Notice to applicants, Vol 3C, 3Ca, 1987)
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMA/CHMP/EWP/147013/2004)
- The investigation of drug interactions (CPMP/EWP/560/95)
- Position paper on terminology in Pharmacogenetics (EMA/CPMP/3070/01)
- Reflection paper on pharmacogenomic samples and data handling (EMA/CHMP/201914)
- A guideline on summary of product characteristics (EMA/CHMP/64302/2005)- Rev.1
- ICH Topic E 15: 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/56776/2006)

2. SCOPE OF THIS PAPER

The following issues are discussed in the document:

- Summary of EMA experience of PG information in oncology (Jan 2000 - Dec 2007)
- Experience from the scientific advice procedure (2005-2006) and from EMA-PGWP) voluntary briefing meetings on oncology products
- Considerations in relation to need for special/specific diagnostic tests
- Suggestions for data representation in the product literature
- Anticipated data for future applications

The discussion will include considerations on the followings

- PG markers in clinical pharmacology studies & design
- PG markers in pivotal efficacy and safety studies
- Implications for diagnostic or PG marker test availability

3. SUMMARY OF EMA EXPERIENCE OF PG INFORMATION IN ONCOLOGY (CENTRALISED PRODUCTS)

Between 2000 - Dec 2007, the EMEA and its scientific committee, (CPMP/CHMP) reviewed data on 26 new medicinal products for the treatment of cancer that passed through the centralised marketing authorisation (MA) application process. Of these, 7 were for leukaemia/lymphomas, 3 for breast cancer, 3 for colorectal malignancies, 2 for lung cancer and rest for various other cancers. A number of biomarkers were examined in the developmental phase of these agents including clinical pharmacology /pharmacodynamics, relation to efficacy in pivotal trials and in certain cases, targeted therapy. Information regarding attempts at identification of the target population using specific biomarkers has been the most consistent approach in majority of applications, especially in pivotal studies. These included the conceptual basis of the proposed mechanism of action (particular molecular target of the medicinal product), identification of the target population using specific tests (or PG information) such as the presence of a biomarker and lastly, the use of a biomarker in recognising the response or remission of the clinical conditions/malignancy.

In ~20-25% of the centralised applications for products relating to oncology (n=6) that were evaluated by CPMP/CHMP between the years 2000-2007, the data were sufficient to permit inclusion of important PG information in relation to one of the following; clinical pharmacology (the mechanism of proposed action), the identification of the target population and, as a measure of efficacy or safety of treatment. The applications included many of the following disease situations; lymphomas, breast cancer, lung cancer and colorectal cancers. While there were several biomarker related to cancers in published literature (such as association of Philadelphia (Ph¹) chromosome and chronic myelogenous leukaemia), within the regulatory context, Her-2 receptor overexpression in cancer cells is the first biomarker to be accepted as basis for the approval of a therapeutic indication in the breast cancer population.

The effort to substantiate growth factor related biomarkers, phenotypes or genotypes appears to be the major or common theme in the datasets available so far from the centralised procedures and herein lies the focus of pharmacogenomics in oncology. The relation between the epidermal derived growth factors, their receptors and tumour response to treatment in cases of breast, lung or other cancers are well recognised both in the scientific and regulatory context through data submission to the EMEA. Examples of these include regulatory history of trastuzumab (Herceptin®), cetuximab (Erbix®), lapatinib (Tyverb®) and panitumumab (Vectibix®). Patients with Her-2 positive breast (20-30% of all cases of breast cancer) had poorer outcome than those who were Her-2 negative. Similarly, EGFR (epidermal growth factor receptor) is frequently over-expressed in advanced colorectal cancers (up to 80 % of subjects with colorectal carcinoma), and higher levels of EGFR appear inversely related to survival.

The overexpression of Her-2 or EGFR receptors, have served as targets for treatment in addition to being important markers of disease. The discovery of targeted monoclonal antibodies (mAbs) to specific antigens has had a major impact on diagnostic and prognostic aspects of pharmacogenomics in oncology. Within the data available, so far there is a preponderance of instances where the monoclonal antibodies against specific targets determined the response to treatment with improvement in progression free or overall survival. Trastuzumab was the first mAb against ErbB2 (Her-2) receptor, which provided prognostic benefit in both patients with advanced and early breast cancer.

The recognition of EGFR expression on tumour cells during early studies combined with development of targeted monoclonal antibody at the EGFR receptors, lead to the subsequent observation in pivotal studies that the EGFR expression was a marker for tumour response to treatment with cetuximab in patients with metastatic colorectal malignancy. Cetuximab is a mAb against the extracellular domain of the EGF receptor (EGFR) and acts as signal transduction inhibitor.

Biomarkers may also identify a more specific patient population that does not derive benefit from conventional treatment and promote further targeted therapy. Lapatinib, a dual inhibitor of ErbB1 (EGFR) and ErbB2 (Her-2) demonstrated benefit in the treatment of patients with advanced or metastatic Her-2 overexpressing breast cancer who had previously received other anticancer therapy including

trastuzumab. Recent approval of lapatinib is thus an example of identification of a very specific target population.

Another example of a product for whose use a biomarker helps identify a specific population is panitumumab (Vectibix®) and this was approved recently. Panitumumab is a IgG2 mAb directed against the human EGFR and inhibits tumour growth. KRAS oncogene mutations are common in cancers of lung, pancreas or colon and are known to encode a protein that remains in the active state thereby transducing downstream signals continuously. The wild type KRAS genotype (non-mutated KRAS) identifies the population with advanced colorectal cancer which is likely to benefit from panitumumab while the mutant variety had a less favourable outcome. Indeed in the overall population the benefit was not clear. Trials are under way in VEGF expression in several other oncological conditions and results are awaited. The process is however still in the early developmental stages.

Certain chromosomal aberrations in malignant cells (or certain genotypes) also have the potential for identifying a target population that subsequently evolves into a subgroup to demonstrate advantages of a given targeted treatment in relation to efficacy or safety. For example, Arsenic trioxide (Trisenox) has shown greater benefit in those patients with acute promyelocytic leukaemia who carry the t(15:17) translocation and or PML/RAR-alpha gene (promyelocytic leukaemia/Retinoic acid receptor alpha). In this context, it is of interest to note that response to retinoids may also be determined by chromosomal aberrations (t11:17 translocations are resistant) this however was not part of the centralised approval process within the time span specified for this document.

Such data have been valuable and lead to inclusion of “PG information” in the product literature; for example, trastuzumab is indicated in those with Her-2 positive breast cancer, cetuximab indicated for EGFR expressing colorectal cancer while panitumumab is specifically indicated for EGFR positive advanced colorectal cancer with wild type KRAS. In case of trisenox, it is indicated for acute promyelocytic leukaemia in the presence of either t(15:17) translocation or PML/RAR-alpha gene.

4. RECENT EXPERIENCE FROM THE SCIENTIFIC ADVICE PROCEDURE (2005-2007) AND BRIEFING MEETINGS

4.1 Scientific advice procedure

Products relating to oncology have recently occupied a fair proportion of scientific and regulatory advice to industry through the scientific advisory working party (SAWP) of the CHMP. In the years 2005-2007 (years prior to drafting this reflection paper), 89 oncology related advices (indication specific) passed through this process. Due to the large number of scientific advices that the SWAP deals with and in order to capture more recent developments, the paper examined only 2 years prior to drafting of this paper. Moreover, it was anticipated that earlier scientific advices (before 2005) had already resulted in either grant of MA or lack of impact on approval or product information.

The advices related to use of specific PG information for ‘patient selection or diagnosis’ or use of various biomarkers in early and pivotal studies as indicators of efficacy or safety. It is recognised however that PG in oncology is being explored on many other directions but the current paper reflects only those products which were dealt with in SA procedures. Overall, 13 of the scientific advice (15%) requests had information about proposed specific indicators or markers for either patient selection or diagnostic parameters. In six others, development of certain potential biomarkers were included or proposed. Advice regarding the appropriateness of such diagnostic characteristic or biomarkers was sought. Of these 13 scientific advice requests that contained PG information, majority involved various tyrosine kinase inhibitors or closely related pathways. This indicates a trend in the oncology field to extend the scientific advice opportunity to the use of genomic knowledge beyond its impact on pharmacokinetics alone.

4.1.1 Examples

It should be recognised that the patient characteristic /specific indicator varies and the characteristic may take several forms. These based on data submitted have so far included the following;

- chromosomal aberration [*ph+ chromosome CML; multiple myeloma with t(4:14) translocation*],

- point mutation in tumor specific oncogene (*T3151 mutation in BCR-ABL kinase domain- FTL3 mutation in AML*),
- genomic overexpression (*C-Kit gene sequencing for mastocytosis; EGFR or Myc gene overexpression and ENT2 transporter, increased EGFR gene copy number in NSCLC*), or receptor overexpression (VGFR receptors in various cancers, ERB2 receptor overexpression in breast cancer).
- certain antigen expressions such as MAGE-A3 (melanoma gene, family –A3 could indicate suitable candidates for specific intervention).
- other proteins (or transcription factors) associated with gene expression such as anti-apoptotic protein Bcl-2 [*nf-κB and follicular NHL*].

In certain situations vaccines directed against a particular protein or cellular component may also be useful. Indeed for studies using agents whose biological mechanism and relation are very well established (for example EGFR +/- tumours and agents influencing their activity), there is an anticipation that these will be used consistently and such data would be expected to be part of the dossier for marketing authorisation.

Certain common themes that emerge from the CHMP scientific advice discussions are:

- specific enrichment of biomarker positive patients in clinical trials has been considered acceptable.
- identification of a specific responder subpopulation to include in a clinical trial might make future developments more complex as the need to use an appropriate comparator for such a segment of the population becomes crucial. On the other hand, this would encourage development of treatment for other segments of the population who were not responsive to earlier approved treatments.
- the preferred end points in oncology clinical trials should be overall survival although other end points such as progression free survival may be acceptable in the case of very narrowly defined refractory population (based on PG);
- A single study combining retrospective/exploratory hypothesis and validation steps of a genomic biomarker together may be acceptable. However for approval purposes confirmation of the true value of the effect in the segmental population shall be confirmed prospectively in a second clinical trial.
- The inclusion of biomarker negative population in the development programme in the current context will depend on the knowledge available for the specific target in question. Caution is advised in relation to identifying a PGBM that provides a biological basis for the mechanism of action. In such situations the assay should be sensitive, specific and reproducible. During the clinical development analytical and clinical validation of the assay performance shall be provided e.g. with confirmation in a central specialised clinical laboratory. If these conditions are satisfied for the PG BM, it would also be necessary to provide adequate justification to include BM negative patients in clinical studies when a benefit is not expected in this subgroup.

To elaborate, one of the considerations is use of PG information or PGBM for selection of patients. This has to be in the specified context. For example using EGFR status to stratify or target a subpopulation in patients with a particular type of cancer might be valid and the entire population (FISH +/- for EGFR) may not be included in all studies. If benefit is demonstrated in a subset only (BM positive vs BM negative), extrapolation of these results to the overall population (i.e., unrestricted) would require further confirmation in additional study(ies). A particular example is in ISEL study where a trend for benefit in EGFR positive patients was seen but overall survival in the entire group, EGFR+/-, for was not different to placebo [[Iressa \(gefitinib, ZD1839\)](#)]. However, the subsequent study, INTEREST did not confirm these results of differential benefit dependent on EGFR status [[Interest-trial](#)] although the two studies aimed at slightly different populations (first line and second line treatment of NSCLC respectively]

Another aspect that arises out of the scientific advice experience relates to the commercial availability of assays to identify highly specific target populations (e.g., multi-agent resistant tumours). It is anticipated that for such situations, a valid commercial assay should be available (as a pre-requisite to a MA). In EU a diagnostic assay will have to comply with the requirements laid down in the IVD Directive (98/79/EC; ref OJ No. L331 7.12.98 p.1). In addition, depending on Member States public health arrangement for the use of in-house validated PG testing in reference specialised clinical laboratories may be made available.

4.2 *Experience from CHMP/PGWP Briefing meetings or other regulatory aspects;*

Since the constitution of Pharmacogenomic Working party of CHMP in 2005 (and the Ad-hoc group prior to 2005), both industry and competent authorities have sought advice from this Working Party in relation to PG information impacting product information for both existing and emerging products. Some of these provide excellent examples of impact of PG information on the product literature and sometimes clinical utility. It is of interest that in many instances PG information relates to genetic polymorphisms (especially single nucleotide polymorphisms, SNPs). The polymorphisms may impact on aspects of medicinal product's pharmacokinetics, pharmacodynamics, efficacy or safety. Toxicity of certain medicinal products may be enhanced by genetic polymorphisms in the hepatic enzyme pathways that either increase the exposure to the agent (increased C_{max} and AUC) or to a specific metabolite (potent active or toxic). These include irinotecan, DPD inhibitors with 5 FU and impact of TPMT mutations on mercaptopurine use. The common examples where data are available relate to safety aspects^{6a, 6b} (e.g., UGT1A1*28 allele and irinotecan) and mercaptopurines and TPMT mutations. (See section 5)

Irinotecan is a topoisomerase-1 inhibitor indicated for treatment of metastatic cancer of colon or rectum. Recent developments have suggested an association between UGT1A1*28 alleles and neutropenia^{6a, 6b}. The irinotecan issue was discussed at the pharmacogenomics working party. The expert group concluded that data were insufficient to reliably assess the predictive value of UGT1A1 7/7 polymorphism on the need for an altered dosing recommendation to reduce neutropenia but the association was considered suggestive. Furthermore, the reliability of bilirubin as a BM for homozygous UGT1A1 7/7 genotype in patients with cancer especially liver metastasis was questionable. For either of these, the positive predictive value (~50%) was considered too low for inclusion of definitive statements in the product literature.

DPD (Dihydropyrimidine dehydrogenase) is the rate limiting in the catabolism of 5-FU. Toxicity of related to 5-FU has recently been related to DPD deficiency and a number variant alleles (of DPYD, gene encoding DPD) have been identified. There however are limited data in terms of a clear relation that is likely to influence inclusion of PG information in the product literature. There have been suggestions that use of a DPD inhibitor could reduce the toxicity of 5 FU by achieving a reduction in dose. Confirmatory data are awaited for both these situations before definitive conclusion and regulatory recommendations could be put forward.

5. DEVELOPMENTS OUTSIDE OF CENTRALISED/SCIENTIFIC ADVICE PROCEDURES OF EMEA

5.1 *Information in the Public domain*

Recent developments in PG information (such as published literature) outside the areas of centralised authorisations have an impact the regulatory knowledge and process. The products involved are likely to be national authorisations in EU [or worldwide] but advances in PG information in relation to such products have a significant regulatory interest and impact. Several such instances have indeed been brought to the attention of European commission, EMEA/EU competent authorities. For example: tamoxifen, CYP2D6 polymorphism and clinical outcome, or the TPMT mutations and mercaptopurine in treatment of ALL. The latter was the subject of a European commission initiated project in all EU member states that analysed the cost effectiveness of screening for TPMT mutations. While these products were outside the scope of centralised authorisation process and a detailed discussion of these is outside the scope of in this paper, they are however considered of sufficient scientific importance. These matters concerning medicinal products approved nationally are discussed at the level of the National Competent Authorities in the member states.

As mentioned before in these instances the PG information often relates to genetic polymorphisms (especially single nucleotide polymorphisms, SNPs) impacting on aspects of medicinal product's PK, PD, efficacy or safety. There may be increased exposure to the agent or the metabolite with consequent unanticipated effects. One particular example is the recent development with tamoxifen an already established product authorised nationally within the EU. Tamoxifen is well established in the treatment of oestrogen receptor positive breast cancer and the metabolite, N-desmethyltamoxifen (NDM) plays an important role. Recent studies suggest that a further metabolite of NDM, endoxifen impacts on the

clinical outcome or adverse event rates^{7a, 7b} and its generation is dependent on CYP2D6 genetic variants or concomitant use of CYP2D6 inhibitors agents (e.g. paroxetine)^{7b}. SNPs (or mutations) that inactivate or reduce CYP2D6 activity are therefore likely to influence the overall risk:benefit ratio by producing less metabolite. For example, those patients with CYP2D6 inactivating polymorphisms (*4, *5, *10 & *41) who were poor or intermediate metabolisers had higher risk of relapse or death in two studies.^{7c, 7d} In contrast, CYP2C19 *17 variant, which implies an increased production of active metabolites apparently identified those likely to benefit.^{7d} As some of these may be retrospective analyses, such instances require careful consideration of the data available and handling through an appropriate regulatory process.

Another example comes from the TPMT alleles (thiopurine methyl transferase) and mercaptopurine therapy. TPMT catalyses s-methylation of mercaptopurines there by initiating the inactivation process. Heterozygous individuals have intermediate activity and homozygotes for mutant alleles (TPMP*2-*18; n=20 alleles, most frequent *2 & *3) have low TPMT activity and accumulation of thioguanine nucleotides leading to toxicity. The TPMP issue is included here as this formed a EU wide cost effective analysis project to assess the impact of screening for these mutant alleles. Implementation of these findings is in the domain of individual member states that may result in inclusion of certain information in the product literature.

From the regulatory point of view, the associations highlighted above will need to be robust and validated. Observational studies /data or association studies alone may not be adequate to provide a basis for a regulatory action such as inclusion of PG information in the product literature (SPC/label).

6. BIOMARKERS/ TESTS & TESTING METHODOLOGY

6.1 *Characteristics of Potential markers*

Based on the experience gained so far, certain characteristics could be described for an ideal marker. The important factors in relation to biomarkers and disease characteristics or drug response in either the scientific advice or regulatory approval process include,

- identification of the characteristic that is measurable and quantifiable with a certain degree of consistency,
- demonstration of a relation between the marker and the disease mechanism or progression, the pharmacological actions of a medicinal product. These are usually obtained from pre-clinical or early clinical studies (phase I-II).
- validation of the characteristic or the biomarker in relation to the parameters discussed above in phase II and phase III trials or by epidemiological methods.
- Availability of a testing or identification platform. These could take several routes including, histology, immunohistochemistry, fluorescence testing or other imaging modality.

6.2 *Points in relation to special /specific tests;*

In the study of how genetic variants influences the drug response (pharmacogenomics), recent years have seen a great progress. A variety of characteristics are potential candidates to act as indicators of this influence. In order to identify the special characteristic (receptor overexpression or gene overexpression or recognition of an SNP), often specific tests may be needed that must have the required specificity and sensitivity. A number of testing platforms are available that are dependent on the genomic biomarker of interest. The testing methods may include cytogenetics, microarray techniques, PCRs (or RT-PCR), southern or northern blots, western blots for particular protein markers or others. Some of these have common methodology while others may be specific. For example, immunohistochemistry is one the techniques used in the development of trastuzumab. This has been superseded by FISH (fluorescent in-situ hybridisation) and more recently by CISH (chromogenic in situ hybridisation) techniques. CISH technique has certain advantages over the FISH but it is beyond the scope of this paper to discuss the relative benefits.

On occasion, when two of the factors (such as a disease characteristic and /or gene overexpression or any other combination) occur together, a combination of tests/platforms may be required. For example, detection of Philadelphia chromosome (Ph+) will be based on cytogenetic tests while T3151 mutation is likely to be either an extension of this or another platform. It is therefore anticipated that the platform

used/employed will depend on the type of information to be obtained and the platform may be specific to that marker or non-specific.

Based on the information available to date from the centralised application process, a number of test/platforms have been used although the FISH/CISH methods and cytogenetics have been the predominant platforms. Examples of successful applications or tests specified in the product information (SPC) are; (i) identification of the Ph⁺ CML patient and (ii) use of FISH/CISH for Her-2 receptor status. Other clinical trials are underway using similar platforms. Similarly, for cetuximab (erbitux) indicated in EGFR positive metastatic colorectal cancer, all clinical studies utilised the Dako Cytomation test to assess the EGFR status. Alternative methods/assays for EGFR status were not tested in that development program.

6.2.1 Test characteristics

Consequent to the experience to date in both the centralised authorisation process and the CHMP scientific advice, there are certain features that a test or platform is expected to fulfil from a regulatory perspective;

- The platform/test should have a level of general methodological validity/ consistency. The validation of its specificity to the clinical issue in question is expected to come from the clinical trials conducted in that particular condition.
- The platform/test should be sufficiently widely available in order for it to be feasible to be used in the developmental and clinical phases.
- If considered a diagnostic test, it should fulfil the EU requirements of diagnostic tests or agents.
- In certain situations, there may be necessity to specify the type of test/platform and the kit required to perform the test. This may imply that when the product or PG information is to be used in clinical practice, it is anticipated that the platform /test shall be available without restriction for such use.

7. IMPACT ON PRODUCT INFORMATION (PRODUCT LITERATURE)

Several areas in the product information could be influenced by the PG information including the indication, posology, warnings, adverse events or mere inclusion of PG information in pharmacodynamic section.

Of the 26 new products for oncology seen by EMEA in the centralised process between 2000-2007, the dossiers on 6 medicinal products carried adequate data in the preliminary and pivotal studies that impacted the product information. The initial studies identified the proportion of the overall population in a particular disease entity (e.g., 30% subjects with breast cancer have Her-2 overexpression or ~80% have EGFR overexpression in colorectal cancer). The subsequent pivotal study data confirmed the importance of PG testing in terms of clinical benefit leading to inclusion of specific PG information in the product literature. The lapatinib SPC included information regarding the specific population where benefit was derived (Her-2 overexpressing individuals who had been previously treated) and this was critical. In addition, one other MAA has been reviewed by CHMP (panitumumab- Vectibix) that not only influenced the opinion but also the information included in the SPC/label.

The indication for Trastuzumab specifies its use only in those with confirmed overexpression of Her-2 receptors in accordance with the available data from pivotal studies. Immunohistochemistry using tumour tissue samples was the initial platform that subsequently evolved to detecting Her-2 receptor gene amplification using FISH or CISH testing. These are included in the trastuzumab SPC. In an analogous scenario, the SPC of arsenic trioxide (trisenox; approved centrally) for acute promyelocytic leukaemia, identifies presence of t(15;17) translocation as indicative of improved efficacy. In this instance molecular remission using RT-PCR was achieved in 51% during induction and 78% after consolidation phase. Cetuximab is an example of a specific testing Kit used consistently in all clinical trials to determine the EGFR status of metastatic colorectal cancers. For panitumumab, the indication has been specified as those without KRAS mutation in tumour cells. Of note it is the absence of the KRAS mutation (or the presence of wild type KRAS oncogene) that offers the benefit.

In general, the following are likely to govern the inclusion of PG information and impact the PG information will have on the product literature;

- a clear, demonstrable relation between a patient biomarker with either the disease progression or drug response in early phase studies,
- validation of the biomarker with disease progression or drug response in phase III clinical studies. This may include enhanced efficacy or altered safety profile related to presence or absence of the biomarker,
- the availability of the testing platform in general,
- the ease and the ability to perform the test and evaluate the marker for the consequences in clinical practise.

8. ANTICIPATED DATA REQUIREMENTS FOR FUTURE APPLICATIONS

The field of pharmacogenetics/genomics and drug regulation is still an evolving area. Any PG information relating to a medicinal product in terms of efficacy or safety has to have the required scientific rigor before this could be considered in the regulatory process. At the present point in time, the data requirements would at the very least be dependent on the following;

- the scientific basis for the marker
- the clinical condition being studied
- the relevance of the chosen marker in the condition being studied
- the nature and reliability of the marker selected for analysis
- demonstration of a consistent, reproducible, specific relationship between marker and the condition being studied,
- demonstration of a reliable, consistent relation between the marker and drug response in terms of dose/response curve, efficacy and adverse event of a particular medicinal product (class of medicinal products).

Based on the described experience, the following aspects shall be taken into consideration in a development programme;

1. Clear demonstration of scientific basis for choice of the marker
2. Data from in vitro and pre-clinical studies could be supportive of the concept.
3. Phase I-II studies demonstrating consistent relation of the medicinal product with
 - Dose-PD response relationship in a defined subgroup/population
 - Either a claimed effect (benefit) in defined subgroup/population- using an identified marker
 - Or an adverse event/s in that defined population (should be consistent & specific)
4. Confirmatory evidence in an adequately defined study subset.

The data /should also address the requirements for biomarker and the test used /proposed for assay as discussed above.

The responsibility for such a demonstration lies with the applicant. It is also anticipated that the applicant would adequately investigate the plausible mechanistic backgrounds for any effect/benefit or safety issue demonstrated. Information may be derived from association studies, but these are unlikely to be considered pivotal or adequate to define the relationship sought above.

Factors affecting clinical studies for evaluation of PGBM;

Based on the current EMEA experience, it is advised that the applicant /company pay specific attention to the following aspects in designing clinical studies that involve evaluation of BMs in relation to pharmacogenomics: in general the development programme should include the overall population of both biomarker positive or biomarker negative patients; enriched population studies may be considered depending on the clinical situation; adaptive design studies that assess the null hypothesis in biomarker positive patients progressing on to the overall group (BM positive or negative) may be considered; and the preferred end points for the phase III trials in oncology are overall survival. However other end points (such as progression free survival, time to treatment failure etc) may be applicable but should be fully reasoned and justified.

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Abbreviations:

AML	Acute myeloid leuemia
BCR-ABL	Breakpoint Cluster region of ABL(Ableson) gene
CHMP/CPMP	Committee for Medicinal products for Human Use
CISH	Chromogenic in situ Hybridisation
CML	Chronic myeloid leukaemia
CYP2d6	Cytochrome P450 isoenzyme- 2D6
DFD	Dihydropyrimidine dehydrogenase
EGFR	Epidermal Growth factor Receptor
EMA	European Medicines Agency
EWP	Efficacy Working party
FISH	Fluorescent in Situ hybridisation technique
ICH	International Committee for Harmonisation
mRNA	messenger RNA
NDM	N-desmethyiltamoxifen
NHL	Non-Hodgkins lymphoma
NSCLC	Non-small cell lung cancer
PCRs	Polymerase chain reactions
PG	Pharmacogenomic
PG BM	Pharmacogenomic biomarker
RNA	Riboneucleic acid
RT-PCR	Reverse transcriptase- PCR
SNP	Single nucleotide polymorphism
SPC	Summary of product Characteristics
SSRI	Selective serotonin reuptake inhibitors
UGT1A1	UDP-glucuronosyltransferase enzyme
VEGF	Vascular Endothelial Growth Factor