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Report on the EMEA/EFPIA Pharmacogenetics Workshop on Integrating Pharmacogenetics Early into Drug Development: PK as a working example

December 19th 2008, EMEA Canary Wharf London

Overview:

This was the third in a series of EFPIA/EMEA one-day open workshops. On this occasion, the workshop focused on the application of Pharmacogenomic (PGx) biomarkers in early clinical drug development (from Phase I to Phase IIa). Pharmacokinetics (PK) in drug development was used as an example as it presents a familiar drug development context with well-established regulatory processes, and industry best practice for data analyses. In addition, there is an accepted evidence-based set of PK phenotypes associated with genetic variants particularly in the metabolism pathways of Adsorption, Distribution, Metabolism and Excretion (ADME), which were used as the basis of the case studies.

The Workshop was co-chaired by Prof. Bruno Flamion, Chair of the CHMP Scientific Advice Working Party (SAWP) & Vice-chair of the Pharmacogenomics Working Party (PgWP), and Dr. Duncan McHale Chair of the EFPIA Pharmacogenomics team. A wide range of experts was present, including representatives from Regulatory Authorities, Academia, Industry, and external organizations.

Workshop Goals:

- Establish areas of consensus among Regulatory Authorities, Academia, Industry and other relevant stakeholders in the appropriate application of PGx in drug development to improve understanding of PK variability;
- Identify areas where additional discussion would add value to a guideline currently being drafted on the use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products;
- Provide an opportunity to raise awareness of PGx among non-specialists on the current state-of-the-art thinking.

Workshop Process: Four sessions over one day, which involved:

1. Review of current experience with the use of PGx in PK evaluations from the EMEA, PMDA, FDA and Industry;
2. Case studies using PGx-PK analyses from Phase I to Phase IIa discussed in breakout sessions;
3. Overviews of the needs to ensure PGx data are useful to the prescriber;
4. Panel discussion.

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Executive Summary:

The workshop went beyond its proposed goals for the day in a very successful way, as evidenced by the following outcomes and key messages:

Workshop Outcomes:

1. EMEA initiated an action that they would organise a small multidisciplinary core group to work on their 'PGx in PK' guideline, which builds on their 2007 reflection paper (*Reflection Paper On The Use Of Pharmacogenetics In The Pharmacokinetic Evaluation Of Medicinal Products; EMEA/128517/2006*) and which will be available for public consultation in 3Q09. EMEA draft authors (Dr. Marc Maliepaard, the Netherlands Medicine Evaluation Board Agency and Dr. Magnus Ingelman-Sundberg, Karolinska Institute) have agreed to the principle of holding discussions with industry and external experts to address areas of concern.
2. Awareness was raised on all sides of the challenges and opportunities faced by stakeholders in developing new medicines. For example, regulatory agency attendees gained awareness regarding the types of challenges in clinical trial decision-making in the face of the substantial unknowns and uncertainties, which are integral to early drug development. Similarly, Industry attendees received insight into the needs of regulators for robust, reproducible results of high quality to facilitate decision-making.
3. After the workshop, there was agreement by EFPIA and EMEA for public dissemination of the workshop proceedings to share content, key points to consider and next steps via websites as well as a peer-reviewed publication.

Key messages for next steps:

- Although PK was used as a workshop example, a consistent message over the day was that this endpoint should not be considered in isolation. Hence while an initial PGx effect may be observed with PK, a broader interpretation that includes downstream clinical effects is required to develop a new medicine. Ideally PGx knowledge is integrated with other covariates into a model-based assessment, which then may (or may not) predict efficacy and safety in various populations and in different disease states.

- Drug-Drug-Interaction (DDI) clinical trials are conducted frequently as part of early drug development programmes. DDI is an example of how PGx data is 'actioned' or integrated in the context of early drug development. Thus evaluation of PGx in PK facilitates current DDI, for example by prioritizing the number of clinical scenarios tested.

- The extent of DNA collection in clinical trials remains an open question, as not all clinical trials in drug development will have relevant clinical data that can be used to make valid associations with PGx. Thus collecting samples that will not be used adds to the already substantial costs of Good Clinical Practices (GCP) which are required in regulated drug development ranging from DNA sample storage, clinical data storage, quality assurance and quality control, to ethical procedures including security that ensures ongoing privacy and confidentiality for study participants.

WORKSHOP DETAILS:

Session 1: PGx in PK from Various Perspectives:

Dr Marc Maliepaard (MEB & CHMP/PgWP)

Dr Maliepaard provided an overview of recent experience of the CHMP in reviewing PGx data submitted in support of PK investigations. He stated the intention of developing a guideline on PGx studies of PK variability, which will be released for comment in 3Q09. He noted that the full extent of metabolism for a new chemical entity (NCE) is usually studied late during development. Similarly understanding the influence of PGx happens later in development.

From a regulator's point of view, early understanding of the influence of PGx on PK could help improve decision-making during development and registration.

Thus, there are needs to:

a) Move beyond CYPs and UGTs. Transporters are becoming more important, *e.g.* SLCO1B1 and response to statins;

b) Evaluate genotyping platforms like the DMET chip;

c) Encourage genotyping in Phases I, II and III.

Dr Brian Spear (Abbott)

Dr Spear presented Industry's experiences with PGx in drug development and expectations from the workshop. The latter included a desire for greater understanding of the regulators' expectations as to:

- When PGx investigations should be performed as part of a drug development program in order to understand drug exposure;
- How PGx data will be interpreted with respect to PK and other relevant co-variates;
- Collaborative process on guidelines and other European regulatory documents.

Dr Yoshiaki Uyama (PMDA)

Dr Uyama presented an update on PMDA experience and likely future directions of PGx in Japan.

There are currently specific PGx guidelines published by the PMDA:

1. Apr 08: Evaluating genotyping platforms based on DNA chips;
2. Sept 08: Guiding principles on clinical trials using PGx;
3. Next: Clinical trial design using PGx, PGx Test Availability/Co-Development, Data handling in approval process (with a possible focus on ethics focus).

In addition to the published guidelines it was noted that the PMDA has been an observer to the Joint EMEA and FDA voluntary genomic data submission (VGDS) meetings since 2007, and is planning to set up a similar process within the PMDA.

Other important points noted were that the Japanese NHI scheme reimburses 8 PGx tests and tests are advised in local Japanese product information. Recent data has highlighted that PGx variants can affect Caucasian populations differently from Asian populations so it may be difficult in some cases to generalize one group to another *e.g.* allele frequencies, UGT1A1, HLAB* 1502.

Dr Larry Lesko (FDA)

Dr Lesko provided an overview of recent experience at the FDA and the likely direction of PGx applications, stating that a new FDA guidance on PGx applications to PK will be released for consultation in 2Q09. This guidance will cover Investigational New Drugs (INDs) and will also include aspects of clinical pharmacology in labeling, *e.g.* all genetic studies in PGx subsection will be in clinical pharmacology and clinical sections.

He described a broadening agency view on PGx analyses in clinical trials beyond 'optimal' (i.e. prospective, well controlled) towards a 'pragmatic' approach (i.e. post-hoc pre-specified analyses of data from prospective clinical trials). Such an approach must be based on:

1) a plausible biological hypothesis,

2) a 'large enough' sample size,

3) DNA collected from a large proportion of subjects,

4) an adequate and pre-specified post-hoc analysis plan, and

5) an assay with acceptable performance.

The representatives from Europe and Japan endorsed this approach as pragmatic for safety, PK and dosing, especially where prospective clinical studies would be difficult or unethical due to safety risks, for example.

Dr Lesko also mentioned that in the FDA's view it is recommended to conduct PGx analyses on for-cause rationale bases such as:

- >25% total clearance down an identified pathway,
- steep dose response,
- inter-individual variation, outliers,
- unexpected or unexplained result,
- differences between racial or geographic groups:

Dr Lesko also noted that DDI studies might reveal PGx effects (*e.g.* proton pump inhibitors) and that if PGx data is looked at in isolation then the contribution relative to other covariates may be inflated.

Finally, he strongly recommended broad DNA collection and informed consent.

Session 1 - Q&A:

Dr. Lesko was asked how the term 'clinical utility' was being defined by the FDA, as some tests, which have been said clinically useful, have not been rapidly taken up in clinical practice. He replied that there is no formal agreement, and views can be different between medical practitioner and regulator. FDA's table of validated biomarkers lists those, which are mentioned in the context of approved drug labels. In his opinion, if PGx data is important enough to be included in a product label then it has 'clinical utility'.

Commenting on Dr. Maliepaard's presentation, Dr. Paul Morgan (Pfizer) challenged the ability to quantitatively predict the contribution of transporters to clinical PK and disposition, because the preclinical data is largely qualitative. Dr. Maliepaard suggested that the pre-clinical information was improving and that it maybe possible to translate into clinical effects. Dr. Morgan indicated that data from knock-out mouse models, such as P-glycoprotein, do not quantitatively predict clinical PK.

Session 2: How and when might PGx in PK be integrated and add value into drug development?

Dr Beena Koshy (GSK)

The speaker provided an overview of the development of a DNA chip containing a consensus set of genetic polymorphisms from genes encoding DMET proteins. This was an across industry initiative and the output resulted in an agreed set of genes and variants where the functional effects were understood. A second set of exploratory variants was described where either the functional effects of the gene or variant were less well understood. The expectation is that this will provide a core framework of markers that Industry can apply in drug development and that diagnostic providers can convert into research and/or clinical diagnostic tools.

Dr Linda Surh (GSK)

The speaker presented the core case study on which all the cases to be used in breakout session 3 were based.

A hypothetical example was chosen to demonstrate key clinical science principles yet also include the type of decision-making and, where possible, data sets, drawn from actual drug development programmes. This core case involved the development of a second-in-class molecule to treat type 2 diabetes mellitus with non clinical data predicting a narrow therapeutic window and showing a high dose limited by toxicity represented by temperature elevation in dogs. The molecule is an antagonist which meant that there is well-established pharmacology that a target occupancy of >80% is needed for effect and thus effective human doses would be expected in the higher ranges.

Dr Surh also provided some context in terms of understanding the relationship of drug metabolism PGx relative to overall ADME pathways; the challenges of identifying significant variability out of natural (often wide) human variability; and that PK cannot be considered in isolation. Thus, even if significant PK variability is detected, to be of value in drug development for patients and prescribers', PK would need to correlate with pharmacodynamics (PD) and then PD needs to show correlation with the key endpoints of drug development which are 'efficacy' and 'safety' of a new medicine.

Session 3: Breakout sessions - Overview of Interactive Cases

The attendees were split into 4 smaller groups to take part in case studies examining strategies to include PGx studies in PK analyses. Case studies 1, 2 and 4 looked at different phases of early development while case study 3 investigated the challenges of combining PGx data across multiple studies and diverse genomic platforms. The attendees of each case study were asked to put themselves in the position of being on the drug development team and deciding upon the PGx strategy for the progress of a new medicine.

Case Study 1 addressed the issue of deciding when to incorporate PGx analyses into the first in human studies where the only data available are preclinical and/or *in vitro* PGx data. There was broad agreement from industry and agency attendees' on the value of collecting DNA in Phase 1 healthy volunteer studies. The audience were more inclined to conduct clinical PGx studies in Phase 1 when *in vitro* ADME typing identified genes with large evidence base of a functional effect in clinical literature such as CYP2D6. There were more varied opinions when genes with a smaller evidence base in the clinical literature (such as transporters) were identified through DMPK.

Case Study 2 focussed on incorporating PGx analyses into the first in patient studies at Phase IIa where some evidence of human PGx-PK relationship was available, but no data on potential PGx-PD relationships.

Diversity of opinion increased as more awareness was raised on whether there was clinical relevance of PGx for specific drug development decisions.

The scenario focused on clinical relevance as well on the costs and rigorous requirements for QA/QC of DNA sampling, which needs to be maintained in order to make drug development decisions and as

part of Good Clinical Practice (GCP) required to industry. Most of the agency attendees indicated the preference for DNA collection in all scenarios.

Case Study 3 concentrated on the challenges of combining PGx data across multiple studies.

As highlighted earlier in the workshop one of the major challenges with using PGx to understand PK in early development is the small study size and therefore combining data from several studies is needed.

The group concluded that quality and reliability is paramount when interpreting PGx data and deciding on what PGx data to report to regulatory agencies.

Some of the early scenarios were more suited to support a PGx briefing meeting rather than the proposed Scientific Advice path suggested in the case study.

Case Study 4 focused on designing the PGx strategy for a phase IIb programme.

After an introduction to the case with underlying pharmacokinetic and related PGx data from a phase IIa clinical study, the development team were presented with a number of scenarios representing typical examples of new information on PD parameters that may become available during drug development including from sources outside a company and that may affect the progression of the molecule and hence PGx strategy.

The team's output gave rise to a number of conclusions:

1. Decisions depend on the context and data available from earlier studies. Emergent data may change dramatically how the data is viewed within a company and thus change PGx planning.
2. For all the different scenarios presented, there was a strong consensus supportive for DNA collection as a minimum in all subsequent phase 2B studies.
3. PGx should not be considered in isolation, but in a context together with many other relevant factors (*e.g.*, PK data, toxicity data, PD data, age and demographic data, etc.).

Session 4: Consensus, gaps and next step

Prof. Munir Pirmohamed (University of Liverpool)

The Speaker discussed the 'Application of PGx in PK in medical practice: how does PGx inform decisions?' and gave an overview of currently approved drugs where PGx data is included in the drug label and/or package insert.

He highlighted that despite the growing number of drugs with PGx data in the label, the use of PGx testing in the clinic or medical practice is still the exception. Reasons were discussed including the limited amount of reproducible clinical utility data generated for many of these drugs (*e.g.* triptiline, tamoxifen, warfarin) and the lack of clear prescribing guidelines which include PGx. Abacavir was given as an example of where PGx testing has taken off more rapidly due to the strength of the evidence base via a clinical trial specifically designed with PGx and clear clinical utility demonstrated prior to label changes in the US and in the EU. Ongoing warfarin studies were also detailed in which clinical utility of the PGx associations are being tested prior to any recommendations for changing the algorithm used in prescribing practice.

Prof. Pirmohamed also commented that hard, reproducible evidence together with co-diagnostics might help PGx to enter more quickly into clinical practice. It is however, important also to consider if a PGx effect is large enough to be clinically relevant.

Panel Discussion and Overall summary by Workshop Co-Chairs:

The panel discussion focused on the participant's observations of the workshop.

Regulators found the workshop very valuable in view of the guidelines currently under development, highlighting that the output of the workshop aligned very well with the draft guidelines although a few areas would require further discussion.

Dr. Maliepaard commented that the Guidelines should be flexible to allow deviations if justified.

It was agreed by the panel that the guideline should include points such as: the importance of phenotype (*i.e*. clinically-relevant PGx); PGx is one factor and should not be used in isolation; early clinical trials may provide limited evidence and sampling should be for rational reasons; post-hoc PGx analyses of clinical trial data may be pragmatic and acceptable in certain circumstances.

Ethical committees can be skeptical of broad DNA sampling for PGx analyses although it may greatly improve the understanding of benefit/risk. Therefore regulatory views on sampling should also be addressed in the guideline with the caveat that studies should always be scientifically justified.

It was agreed that it would be beneficial to have some further discussion with the EFPIA Pharmacogenomics team prior to the finalization of the PGx-PK guideline.

Prof. Bruno Flamion in his conclusive remarks mentioned that using the case studies brought out the lack of clarity in a number of points, *e.g.* - what is 'validated'? -what is 'exploratory' versus 'primary' endpoints? - what PGx data is expected in any regulatory submission for Marketing Authorization?

There is the need for more clarity on expectations.

He also highlighted Dr Lesko's 'Optimal versus Pragmatic' approach to PGx, stressing that the latter is often what happens. Retrospective data analyses can be important due to emergent data and should be considered for inclusion in the guideline. In conclusion, given the need to be careful from discussion to guidelines, he highlighted the need for all interested parties to sit together so that before drafting guidelines principles need to be discussed in smaller focus groups to 'get it right'.

Dr. Duncan McHale (AstraZeneca) highlighted how this workshop was a valuable opportunity to learn and understand each other expectations. Industry is facing real challenges to generating and interpreting the data in the phase I studies. Industry is fully supportive of more dialogue in key areas and of working together to meet the proposed draft guideline timelines.

Conclusion:

This important workshop provided the opportunity for a fruitful and constructive dialogue between all stakeholders. Awareness was raised among all attendees regarding the type of challenges in clinical trial decision-making required facing the substantial unknowns and uncertainties that are integral to early drug development. Active exchanges and dialogue were enhanced by focused breakout sessions.

EMEA have agreed to organise a multidisciplinary core group to help drafting and finalising their 'PGx in PK' guideline.