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Report on the EMEA/CHMP Biomarkers Workshop

The European Medicines Agency (EMEA) in collaboration with the European Federation of Pharmaceutical Industries and Associations (EFPIA) organised a first joint Biomarkers workshop on 15 December 2006. The workshop was co-chaired by Prof. Bruno Flamion, Chair of the CHMP Scientific Advice Working Party and Dr Andre W. Broekmans from EFPIA.

The EMEA had previously held a workshop on Biomarkers with academia and Health professionals on 16 December 2005.

Biomarkers play an increasingly important role in the development of new drugs. As additional variable in the design or end points in clinical trials, it is expected that they will contribute to increase the rate of success of new developments and to expedite the development of drugs. Biomarkers are key in the shift away from the "one fits all" to "the right drug at the right dose in the right patient group" approach. Hence, biomarkers play an important role for scientists and industry in drug development and for regulators in the approval process.

The current views on validation of biomarkers were examined, as well as the influence of pharmacogenomics on new drug therapies. Examples of successful biomarker programs were discussed. The workshop was intended to stimulate interactions between investigators/researchers from industry and the regulators. The morning consisted of an introductory session and three sessions on oncology, cardiovascular and osteoporosis with talks from EFPIA and CHMP senior assessors. The afternoon was dedicated to general topics, including presentations on similarities and divergences between EMEA and FDA approaches, the Innovative Medicines Initiative (IMI) strategic research agenda as it applies to surrogates, general issues around biomarker validation and the EFPIA position paper on this issue.

Introductory session

The chairman of the CHMP SAWP Prof. Bruno Flamion gave an overview of activities within the EMEA and the EU with regards to biomarkers and in addition highlighted how continuous discussion on this topic is taking place within the SAWP. He mentioned the new tool of "conditional approval", the "Innovative Drug Development Think-Tank Group" meetings with Industry and Academia (public conclusion awaited in 1st quarter 2007) and the "Briefing Meetings" of the CHMP Pharmacogenomics Working Party with companies to discuss pharmacogenomic biomarkers. He highlighted the constant marked increase in Scientific Advice (SA) applications in recent years, from 58 procedures in 2000 to 261 procedures in 2006 and expressed the commitment of the regulatory experts for continuous dialogue with industry and academia in the future.

Cancer session

Prof. Hans Winkler (Johnson and Johnson) presented an approach for identification of a set of genomic analytes (response signature) as measure of sensitivity of a tumor to a given treatment. This approach includes identification of analytes which differentiate a responding tumor (cell line) from a non-responding one ex vivo in the experimental setting, and assessment of the validity of the gene signature identified in the clinical setting in exploratory trials. Furthermore he presented statistical approaches to analyze biomarker defined patient groups as co-primary populations in clinical trials.

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The issue how to handle data from a regulatory point of view if significance is only attained in a biomarker defined co-primary population but not overall was discussed.

Prof Andrew Hughes co presented together with Dr Andrew Stone (both Astra Zeneca) new approaches for converting a biomarker to a surrogate. In particular they introduced the concept of using a Surrogate Threshold Effect (STE) methodology, i.e. use a certain level of change in a biomarker that enables the conclusion that there is e.g. a 70-80% probability that it will translate into clinical benefit. Examples presented included imaging biomarkers (e.g. FDG-PET), histopathology biomarkers (Ki67) and blood biomarkers (PSA).

Dr Rafal Dziadziuszko (University of Colorado Cancer Center, Denver) presented pharmacogenomic markers in EGFR-targeted therapy of lung cancer. He presented the positive impact of EGFR gene copy number by FISH and on the EGFR protein expression by immunohistochemistry on the outcome in patients treated with gefitinib. Moreover, patients with EGFR mutations (often gene amplification, in approximately 15% of the overall population) have better response rates to treatment with erlotinib. He mentioned important pitfalls in progressing with the development of EGFR inhibitors in NSCLC such as poor translational components of clinical studies (none prospectively enriched or stratified for biomarkers), neglecting differences in biology according to demographic and clinical characteristics (e.g. smoking, ethnicity) and poor standardization of technologies for biomarker assessment.

Dr Bertil Jonsson (CHMP SAWP, Medical Products Agency Sweden) discussed the use of biomarkers for licensing, in particular the use of biomarkers such as imaging and serum markers as alternative measure of tumor mass. He mentioned that biomarkers are important in selecting the correct patient population and in exploratory trials for early evidence of biological activity, but their use as surrogate endpoints in confirmatory trials is a much more complex issue. However, in settings where progression free survival is acceptable as primary endpoint, biomarkers could be also acceptable as primary endpoint too when validated as proper measure of tumor mass stabilization and growth and when they are unbiased in relation to a class of compounds. Generally, acceptance of biomarkers depends also on the degree of activity of the drug, i.e. it is easier to accept biomarkers for very active drugs. The proposed Surrogate Threshold Effect provided a useful framework to construct the weight of evidence to convert a biomarker into a surrogate endpoint.

Cardiovascular session

Dr Bill Vennart (Pfizer) presented imaging biomarkers for the purpose of registration, in particular discussed the potential utility of carotid ultrasound (CIMT), quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS). QCA, which measures the lumen diameter or the percentage of stenosis, was shown to be linked with coronary outcomes. It is however recognized that QCA can only measure advanced atherosclerosis when the lumen is invaded by the plaque, while it has been shown that the majority of myocardial infarction (MI) events occur in non-stenotic vessels. Moreover, digital QCA appears not to have sufficient resolution to perform adequate comparisons in active control studies. CIMT gives an accurate measure of the thickness of the intima-media layers. Increases in intima thickness are highly associated with risk of MI and stroke, as it has been shown also in LDL and BP trials. IVUS, which permits measurements of both lumen and plaque dimensions, has shown in limited settings good correlation with traditional surrogates of CV health such as LDL cholesterol (LDL-C), but it is agreed that more trials are needed before it can be considered as a potential surrogate marker. According to the Speaker, the use of imaging biomarkers is perceived as particularly relevant in assessing the potential incremental benefit of novel therapies combined with LDL-C lowering therapy in slowing the progression of atherosclerosis.

Dr Gonzalo Calvo (CHMP, Agencia Espanola del Medicamento y Productos Sanitarios, Spain) commented that biomarkers are very important in early development but there are difficulties to use them as surrogate in cardiovascular disease considering the very heterogenous patient population and the role and potential interaction of the multiple background therapies. In addition, it is difficult to determine to what extent the surrogate allows to make reliable comparative benefit/risk assessments with other drugs belonging to either other classes or even with the same mechanism of action. According to his view, seeking a single biomarker as measurement of the treatment effect is unlikely

to be successful in cardiovascular disease. Indeed, clustering of biomarkers to build up predictive models is considered to be a more sensitive approach. He also outlined that licensing based on a single biomarker could be acceptable, but not for the prevention of CV events for which outcome trials are likely needed.

Osteoporosis session

Dr Dominique Ethgen presented opportunities and challenges for validation of potential biomarkers to be used for osteoporosis drug development. He presented the bone strength concept using biochemical and bone imaging biomarkers (Finite Element Analysis derived from QCT imaging) in addition to measurement of bone mineral density only (not sufficiently predictive) and use of fracture endpoints which constitute the main current regulatory requirements for osteoporosis drug approval. He highlighted the challenges of conducting bone fracture studies particularly in comparative trials and in low risk population. Fracture is a complex event and for example patients with low risk of falling are at reduced risk of fracture despite having decreased absolute bone strength. Limitations of currently available biomarkers such as biochemical markers of bone turnover, which are very mechanism of action dependent, and mineral bone density (DXA BMD), which only gives an estimate of bone mineral content but no information on bone architecture and structural biomechanical properties, do not allow valid comparisons between drugs in terms of relative bone strength. Among the best current approaches being explored for bone strength estimates, imaging techniques such as QCT and MRI, and derived Finite Element Analysis (FEA) have been highlighted. If qualified by additional work during the years to come, these types of measurements may provide useful information and could allow valid comparison of drugs with different mechanisms of action. Additional large comparative clinical studies of drugs with different mechanism of action are needed in order to have clinical qualification for the imaging biomarkers.

Dr Fritz Lekkerkerker (CHMP, Medicines Evaluation Board, The Netherlands) presented the requirements in the new CHMP guideline, where it is mentioned that normally 2-year fracture data are normally required but biomarkers can be used for dose-finding studies and, if fracture reduction has been already demonstrated, for new dose regime or route of administration and new indication in men. The difficulties in running fracture studies were acknowledged and the exploration of new biomarkers related to bone strength was appreciated, but it was also emphasized that an eventually established correlation of a novel surrogate endpoint with the true outcome for one product would not necessarily translate into having a validated surrogate endpoint when studying other products.

General

Dr Solange Rohou (Astra Zeneca) presented similarities and divergences between EMEA and FDA regarding early approvals (accelerated marketing authorization and conditional approval).

Prof. Klaus Lindpaintner (Roche) presented the Innovative Medicines Initiative (IMI) research agenda in which identification and validation of biomarkers are very crucial issues. Benefits of the IMI for validation of biomarkers include leveraging pre-competitive knowledge that was previously out of reach, leveraging trial data to reach size for statistical power with also earlier involvement of regulators and increased communication among all stakeholders.

Dr Charles Benson (Eli Lilly) presented criteria to select biomarkers for validation (which) and methods to use for this exercise (how). He described validation as a progressively increasing degree of certainty balanced against risk and explained that the degree of certainty needed in a specific case depends upon many factors such as the product, the therapeutic context and risks of validation. In all cases the progression to validation must always consider the overall benefit/risk ratio.

Dr Geoff Barton (GlaxoSmithKline) presented the EFPIA position paper proposals for surrogate endpoints for use in pivotal trials for marketing authorization. The main proposal is to create a joint Agencies, Industry, Academia Working Group to initiate work on nomenclature, validation milestones and regulatory framework, to establish links with surrogate marker initiatives in other regions and to facilitate regulatory aspects of collaborative research projects.

The general discussion included, among others, the possibility to use adaptive designs to enrich populations where there was agreement that it is acceptable if properly carried out from a methodological point of view. Regarding conditional approval, it was mentioned that it is important to have evidence that data on the surrogate/biomarker would reasonably predict that the unmet medical need is met and that companies should provide reassurance that the postmarketing commitments will be performed.

Conclusions and Future Activities

Overall, the discussions delivered a positive appraisal on the progress observed in drug development when using predictive biomarkers to optimize the understanding of the potential impact of the drug in a given indication and the design of the trials (e.g. dosing, patient population) so that targeted therapies could be delivered - re oncology.
On the other hand it appeared that more fundamental scientific and clinical knowledge is required for the qualification of biomarkers as surrogate endpoints; hence the importance of scientists from academia and industry to share with regulators advances in this direction to ensure a timely uptake of innovation in this area and therefore the commitment from the EMEA to hold future briefing meetings and workshops. Therefore, continuous dialogue among the health professionals, industry and regulators is of paramount importance. The EMEA plans to organise a third meeting on biomarkers with all stakeholders, including industry, in the near future.

The meeting documents will also be made available on the website shortly.

Prof. Spiros Vamvakas and Dr Marco Cavaleri (SAOD Sector/Pre-Authorisation Evaluation of Human Medicines Unit, EMEA) would be happy to answer any queries. Their contact details are:

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