European Medicines Agency

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Report on the EMEA/CHMP Biomarkers Workshop

The European Medicines Agency (EMEA) organised a workshop on ***Biomarkers in the Development of New Medicines*** on 16 December 2005. The workshop was co-chaired by Dr Daniel Brasseur and Prof. Bruno Flamion, Chairs of the Committee for Human Medicinal Products and the Scientific Advice Working Party, respectively.

Biomarkers play an increasingly important role in the development of new drugs. It is expected that they will contribute to increase the rate of success of new developments and to expedite the development of drugs. Also biomarkers are key in the shift away from the "one fits all" to "the right drug at the right dose in the right patient" approach. Hence, biomarkers play an important role for scientists and industry in drug development and for regulators in the approval process.

On 16 December 2006 EMEA hosted its first workshop on biomarkers that looked at the current state of development and application, and how they are being deployed from research to the clinic. 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, learned societies, health professionals and the regulators and consisted of an introductory session, a session on cancer and a session in cardiovascular developments.

Introductory session

Academia, learned societies and health professionals representatives were updated by the CHMP and Scientific Advice chairpersons on current EU regulatory activities which could have implications for biomarkers, the new procedure to provide broader and more in depth Scientific Advice, Pharmacogenetics Working Party briefing meetings with companies to discuss design, rationale and clinical utility of their proposals, and the future implementation of conditional approval. Furthermore, academia, learned societies and health professionals were informed about the place of biomarkers in current CHMP guidelines and of the main objectives of the draft CHMP guideline on clinical trials in small populations.

Prof. Michael Hughes (Harvard School of Public Health) presented the experience with the validation of surrogate endpoints in HIV. He stressed the importance of having a reasonable biological model, sensitive assays, potent treatments, large databases (in particular when treatments are not so potent) and developing methodologies for linking information from shorter-term studies when clinical endpoints are distant in time.

Cancer session

Dr Francesco Pignatti (EMEA) presented the EMEA experience with biomarkers in oncology drug approvals and the revision of the CHMP oncology guideline to include considerations on use of biomarkers throughout the development of non-cytotoxic compounds.

Prof. Thomasz Burzykowski (Hasselt University) discussed statistical validation of surrogate endpoints in oncology and underlined the importance of meta-analysis techniques to look at data from several randomised trials, to study the association between the surrogate and the true endpoint at the trial level.

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Prof. Helgi Helgason (the Netherlands Cancer Institute) presented the background and clinical utility of proteomics in oncology drug development including modern techniques, potential applications in malignant disease for screening, monitoring progression or relapse of disease, treatment monitoring and possible new leads for drug targeting. Furthermore limitations and technical difficulties in reproducibility were discussed.

Prof. Heinz Zwierzina (European Society for Medical Oncology) discussed the role of biomarkers in translational research including successful and so far unsuccessful developments, e.g. anti-EGFR and antiangiogenic approaches and anticancer vaccines. He concluded that it is important to identify subgroups of patients with a high chance to respond to targeted therapy in order to speed up drug development, avoid turning down potentially active drugs and define optimal combinations.

Dr Alexandre Passioukov (EORTC) presented developments in biomarker identification and validation for lung cancer including detection/diagnostic biomarkers and prognostic biomarkers. He concluded that single biomarker approaches have not proven to have a strong potential in lung cancer so far, and it was noted that the future could rather be the use of a set of biomarkers.

Cardiovascular session

Dr Pieter de Graeff (Medicines Evaluation Board, Netherlands) discussed regulatory implications for the use of biomarkers in cardiovascular research. His cautious view was that biomarkers are useful for drug development and risk estimation, but currently not as endpoints for pivotal studies in the cardiovascular field.

Prof. Carlo di Mario (Royal Brompton Hospital) presented the potential and limitations of modern techniques for coronary vascular imaging where biomarkers could become very useful in interventions in atherosclerosis because atherosclerosis is clinically silent until advanced stages.

Dr Francois Alhenc-Gelas (INSERM) discussed genetic variations and genomic biomarkers in cardiovascular imaging including monogenic forms of complex arterial diseases as well as genomic wise scans versus candidate gene approach for cardiovascular diseases such as the ACE gene polymorphism and disease outcome.

Outlook

Overall the prospects for the biomarkers are very positive, although generally the development is still at a very early stage. Scientists are still searching for relevant biomarkers, which also need to be defined and validated. Intellectual pressure should be put on the implementation of translational research early in clinical trials.

Moreover participants were of the view that one bottleneck to development is the preanalytical phase and that prospective sampling of fresh frozen material required for most techniques should be promoted with focus put on methods that improve reproducibility.

Another issue, in particular from the statistical point of view, was the importance of sharing data among companies as required for validation of surrogate endpoints.

The role of biomarkers for safety was briefly mentioned and will require more discussions.

In many areas the trend is to use a combination of several biomarkers, and ways to address multiplicity from a statistical point of view were discussed. At the same time the critical issue here is to establish the role and weight of the different biomarkers within a composite score and to establish the link to the true endpoint. Adequate statistical methods to study the surrogacy of a combination of biomarkers with respect to a true endpoint would need to be identified. It was noted that although application of biomarkers may result in an overall decrease in the size of the trials or the increased use of prespecified subgroups, it is envisaged that the plausibility of the design would be increased.

Future

In order to ensure optimal development and best use of biomarkers to accelerate drug development, continuous dialog among the health professionals, industry and regulators is of paramount importance. The EMEA plans to organise a second meeting on biomarkers with all stakeholders, including industry, by the end of 2006.

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

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