Can we facilitate multinational investigator-driven trials?
Brussels, November 10, 2009

The workshop was opened by Ruxandra Draghia-Akli, Director Health of the Research Directorate General (DG) of the European Commission, who introduced Liselotte Høijgaard, chairwoman of the European Medical Research Council, on behalf of the European Science Foundation. It was stated that Europe needs stronger clinical research to take advantage of all the basic and preclinical studies carried out in European public and private laboratories. In contrast with the underfunded medical research, the initiative of the U.S. President was mentioned, that allocated 1.1 billion dollars to establish the comparative benefit-risk of pharmacological and non-pharmacological interventions.

There is a need however not only to obtain more funds for this area, but also to improve the training of clinicians and the quality of trials in order to achieve more reliable results. Furthermore, procedures for clinical trials should be considerably simplified. For example, one European trial to test a drug on fibrous dysplasia of bone took five years just to start. The excess of bureaucracy caused by the European directive was defined a "hyperdisregulatory syndrome". This does not attract young medical doctors to enter the field of clinical trials because the difficulties encountered are not compensated by adequate career opportunities and publications. This field risks becoming an orphan.

Françoise Meunier, Director General of the European Organization for Research and Treatment of Cancer (EORTC), reviewed the importance of clinical trials and their significance in relation to the development of new drugs, teaching and medical practice. It was stressed that cancer requires large transnational trials with a multidisciplinary approach, independent objective evaluation, optimal choice of controls and increasingly a good connection with accurate genotyping. There is a predominance of industrial trials (64%) over independent non-profit studies (36%). The participation of cancer patients in clinical trials is still too low (<5%), partly because fewer trials are possible on account of the heavy bureaucracy and costs, as shown by the fact that EORTC could start 26 trials in 1995 but only 9 in 2008.

Despite these problems EORTC independent research has made progress, such as larynx preservation in head and neck cancers, the efficacy of temozolamide for glioblastoma, and the increased survival in patients with adult myelocytic leukemia.

There is an urgent need to solve the problem of insurance and the definition of sponsor, to achieve stronger recognition and an optimal legal framework. Clinical research is not a luxury but is an essential need in the field of cancer, where major advances are still awaited. Unfortunately, Europe has lost the leadership because clinical studies have moved to other continents and recovery is unlikely unless remedies are set in motion.

Rory Collins (Oxford University) was very critical about the consequences of the European clinical trials directive that led to a waste of money while at the same time

making any clinical trial very difficult partly because of the different interpretations in different countries. In fact, the directive essentially focused on rules rather than on thinking. Good large clinical trials can change practice and influence industry, as shown by the English ISIS-2 and the Italian GISSI trials, as well as studies on efficacy and tolerability driven by academia with industrial money. The question was raised of the inequality between industrial and independent (non-commercial) studies because both must follow the same rules but only industrial trials can be utilized for the registration of new drugs or new therapeutic indications.

Other problems arising from the European directive are the excess of paperwork to obtain approval by ethical committees, the over-interpretation of non-substantial amendments, the different national policies concerning insurance, and over-reporting of suspected unexpected serious adverse reactions (SUSARS). Particular attention was given to the question of monitoring, which uses up over half of the budget for clinical trials. There should be better control of data flowing to the coordinating centre in order to require peripheral monitoring only when problems arise.

The patients' point of view was presented by Cor Oosterwijk, from the European Genetic Alliances Network (EGAN). Academic independent research is needed because it is more likely to be oriented towards innovative fields, neglected areas, and high patient value. Patient partnership is essential because it adds value to clinical trials by advising about the protocol, and significant end-points, as well as by increasing patient participation. There are also interesting examples of the patients being involved to collect funds to support trials. Patients are also important to overcome the public's negative perception of clinical trials.

The industry view was expressed by Antonio Tataranni and Susanna Del Signore from Sanofi-Aventis, underlining the preoccupation that poorly designed independent studies may damage the industry. Stress was laid on the difficulty of implementing multinational studies, insufficient funding, conflicting data, interference with pivotal clinical trials, false claims and legal issues related to non-compliance. It was admitted, however, that independent trials promote innovative thinking, establish new indications and may include specific subpopulations such as children, pregnant women and the elderly.

The possibility of only one ethical committee for all European countries was suggested, as well as the need to harmonize SUSAR reporting among different countries and the importance of reporting only amendments. Academia and industry should have a single standard.

Frank Wising, director of Life Science 1 of the DFG, reviewed the German programme of funding clinical trials. About 20 trials per year are financed for a total of 30m Euro and an average cost of 1.89m Euro per trial. There is a rigorous two step peer review and support is available only for trials with a high impact on patients. In any case there is no support for trials that may offer interest for the drug industry. There is an agreement with Austria and Switzerland for a single peer review. Also of interest is the teaching programme carried out by the Junior Training Academy on clinical trials. During the discussion, the Italian experience was mentioned that a specific law requires the payment of 5 percent of industrial promotional expenses (except salaries) to establish a fund to support independent clinical trials usually not carried out by industry. The programme has been already running for four years.

Martin Terberger, Head of Unit Pharmaceuticals from the Enterprise and Industry DG of the European Commission had the difficult task of defending the European clinical trials directive. He described the need for strict rules for the 5000 randomized clinical trials conducted in Europe annually, involving half a million patients. The aim of the directive was to ensure patients' rights and safety and at the same time the reliability of data. Because of the problems raised by the directive an impact assessment process is now running in order to decide on revision of the most contested points such as guidelines for safety, monitoring and reporting.

During the discussion it was suggested that the Research and Health and Consumers DGs of the Commission would be better places to establish the rules for clinical trials, to avoid obvious conflicts of interest.

A number of practical proposals came from Chantal Belorgey, vice-chair of the clinical trials facilitating group belonging to the French drug agency AFSSAPS, in order to avoid bureaucracy, work overload, duplication, delays and waste of money. Procedures should be graded according to the level of risk of a clinical trial, which is obviously higher for new drugs than for drugs already on the market. Hospital pharmacies should be authorized to prepare investigational medical products, single international rules for insurance, non-commercial trials should be included in the registration process, centralized procedures for the approval of international clinical trials, SUSARS should not be reported to ethical committees, simplification of monitoring are some of the suggestions.

The clinical trials facilitation group has implemented a voluntary scheme, whereby the authorisation to perform a clinical trial in several Member States can be obtained by applying to a single competent authority. In the discussion it was emphasised that it is important to improve the functioning of the clinical trials directive under the current legal framework through the development of guidelines, for example in the frame of the clinical trials facilitation group.

The view of the European regulatory agency EMEA was expressed by its director Thomas Lönngren. Overall, the network of non-commercial organizations sponsored 20% of clinical trials, with important differences in the various phases - from 11% for phase 1 to 72% for phase IV. EMEA was making an effort to establish a European collaboration among 70 centres for post-marketing benefit-risk assessment through the ENCePP programme. Worry was expressed about the difficulty of evaluating clinical trials carried out in Asia.

The position of ethical committees was discussed by Pierre Lafolie from Karolinska Hospital. It was recalled that ethics requires informed consent from patients based on reliable, clear information. The handling of biological samples requires a harmonized procedure for all 27 European countries. Constant surveillance is important from protocols to publications, avoiding recruiting patients without rigorous calculation of the sample size. The need for infrastructure was recalled and ECRIN was indicated as the organization able to support European clinical trials through all the steps.

Burkhard D. Swik from MunichRe made some considerations on the question of insurance. Insurance is needed not only for patients but also for sponsors, investigators, hospitals, CROs and ethical committees. Harmonization among European States is necessary and rules should be based on a European law.

The last presentations concerned clinical trials on advanced therapies. Amos Panet from the Hebrew University in Jerusalem discussed gene therapy, showing that only two gene therapies were approved out of 1500 trials. Vector production, GLP and GMP laboratories, production facilites and hospital facilities are essential nodes for developing gene therapy. Funding is too limited to cope with the complexity of this advanced therapy.

Finally, Katarina Leblanc and Dietger Niederwieser from the European Group for Blood and Bone Marrow Transplantation discussed problems related to clinical trials with stem cells. In this case too obstacles raised by the directive drew complains because of excessive paperwork, heavier workload and consequent increase in costs. The difficulty of starting a trial was illustrated by the delay of six years between approval by the ethical committee and the beginning of a trial on mesenchymal stem cells.

The discussion was led by Andrej Rys, Director Public Health and Risk Assessment of the Health and Consumers DG of the European Commission and was concluded by Ruxandra Draghia-Akli. ***During the workshop there was general agreement that independent clinical trials are hampered by excessive regulation and there is a real need for simplification. Some of the key points requiring less bureaucracy are monitoring, that should be done at the coordinating centre and only occasionally in the participating centres. Paperwork should be inversely proportional to the level of the risk of the trial, avoiding treating all trials the same way. Simplification also includes the acceptance of a single opinion of one ethical committee for all 27 State Members. Efforts should be made to harmonize the interpretation of the rules in the different member States, particularly as regards insurance, in terms of amounts and duration, as well as the handling of SUSARS and substantial protocol amendments. Independent trials should be of high quality, avoiding excessive use of placebo, non-inferiority designs, conflicts of interest and surrogate end-points. It is the quality of the scientific content and clinical relevance, and not only the administrative aspects that need close attention.***

From a general point of view there is a need to facilitate clinical trials to avoid Europe becoming excluded from drug development and becoming only a passive market, with important loss of knowledge and economic disadvantage. It is urgent to persuade young medical doctors and other experts to consider clinical trials the most important step in the development of new therapies. To this end there is a need for a fund to support clinical trials. This fund should not be occasional but constant, so as to allow the establishment, programming and support of networks and their infrastructures. Support for clinical trials should be competitive and could become a fixed component of the framework programmes. The need to set up an ad-hoc group to establish the size of the fund, and the type of clinical trials to be supported was unanimously acknowledged.

Silvio Garattini, Rapporteur
Milan, November 15, 2009