Workshop on the Benefits of a Simplified and Coherent Clinical Trials Framework in Europe

1 December 2011 – 13:30-16:00
European Parliament – room JAN 6Q1

Hosted and Chaired by Prof. Philippe Juvin, MD PhD, MEP
Organised by EuropaBio and its Clinical Trials Topic Group

On 1 December 2011, EuropaBio and its Clinical Trials Topic Group organised a workshop on the Benefits of a Simplified and Coherent Clinical Trials Framework in Europe. The workshop was held at the European Parliament, and hosted and chaired by **Prof. Philippe Juvin, MD PhD, MEP (France, EPP)**. The objective of the workshop was to bring together a wide range of stakeholder organisations in the clinical eco-system present their views and debate ahead of the publication of the European Commission's proposal for the revision of the Clinical Trials Directive 2001/20/EC (CTD). The workshop attracted more than 100 participants from EU institutions, patient organisations, industry, academia, regulatory agencies and ethics committees.

Prof. Juvin opened the meeting. **Dr. Detlef Niese, Head of Global Development External Affairs, Novartis Pharma AG, and Vice-Chair for Science, EuropaBio Healthcare Council** sets the scene for the discussion by presenting the benefits and key specificities of healthcare biotechnology and highlighting the importance of clinical research for the sector.

As an introduction, **Nessa Childers, MEP (Ireland, S&D)** shared her personal experience with trials on mental health and stressed that the revision of the CTD is a unique opportunity to strengthen the EU's position in clinical research by focusing on improving the framework. Indeed she emphasised that inconsistencies between Member States in the implementation of the Directive led to a lack of realisation of the benefits of a harmonised framework for clinical trials in Europe.

The Directorate-General "Health and Consumers" of the European Commission, represented by **Patricia Brunko, Head of Unit D3 – Pharmaceuticals, at DG SANCO**, went on informing the audience that they are working on the revision of the CTD since 2009. The legislative framework today does not contribute very much to help making the EU an attractive place to conduct clinical trials. Ms. Brunko explained the main issues looked at in the current revision process:

- ✓ Submission and assessment of the clinical trial application;
- ✓ Adaption to risk of trials: adapting regulatory requirements to the risk to patients safety and data robustness; and
- ✓ Global aspects of clinical trials.

The potential options described by the Commission were:

- ➢ A single portal: the option already exists in other sectors and includes the submission of a single package of documents
- ➢ A coordinated approach in the assessment of a clinical trial application: various aspects have to be considered in order to ensure a quick and easy process involving less bureaucracy. Complete centralisation of the process does not seem to be a realistic option since it would require a heavy process and infrastructure as well as a complex timeline; and
- ➢ A clear application dossier.

In terms of next steps, the European Commission will finalise the impact assessment in early 2012 and plans to release a proposal by mid-2012, in line with the original deadline. She stressed that while DG SANCO has a heavy workload, there should not be any delay in the publication of the proposal.

To a question by Prof. Juvin on the role of a single portal, Ms. Brunko answered that while she cannot anticipate the content of the proposal, the portal will be the entry point for the clinical trials application process. If a single portal was to be created, Member States will have the responsibility to organise their review process on the basis of a clear timeline provided by the Directive.

It was finally stressed that an appropriate budget will have to be allocated to the EU for implementation of the future clinical trials legislation.

Views from the different stakeholders in the clinical eco-system:

Flaminia Macchia, EU Public Affairs Director at EURORDIS, presented some key principles that should be central in any research involving human beings: benevolence, autonomy and respect of the person, and universalism. She highlighted that ultimately, research should respond to patients' needs. The quality of the research performed is therefore of utmost importance. Using the specific example of rare diseases, she advocated for more coherence of Ethics Committee's decisions across Member States, particularly in the case of multinational clinical trials, which tend to be the norm in the rare disease field. She stated that ethics decisions should be based on universal principles applicable in all Member States, and beyond. This could increase the predictability of the regulatory process, for the ultimate benefit of those patients who have accepted to take part in a trial. Flaminia Macchia also expressed her support for a single submission and the concept of a 'coordinated assessment procedure' (CAP).

Dr. Christiane Abouzeid, BioIndustry Association (BIA), and Topic Leader of the EuropaBio Clinical Trials Topic Group presented the bioscience industry position on the revision of the Directive. She stressed the need for a simplified and efficient regulatory framework to make Europe a more attractive place for clinical research and the development of new and innovative medicines. . She emphasised the need to streamline clinical trial approval processes by developing and implementing a common standardised Clinical Trial Application (format and content) for all EU Member States, which reflects the requirements in the current European Commission guidelines and does not consist of a cumulative list of all the present national requirements. Ultimately a single dossier would be submitted through a single point 'the EU portal' as proposed by the Commission.

Dr. Abouzeid noted that one of the key outcomes from a review of the legislation is a new process to improve the approval of multi-state clinical trials which should provide for a single submission, a single scientific assessment and a single pan-European outcome. She concluded by saying that EuropaBio and its Clinical Trials Topic Group look forward to collaborating with all stakeholders in the clinical eco-system and working with the European Commission and Members of the European Parliament to retain the competitiveness of the EU as a place to conduct clinical research. Innovation will lead to better outcomes for patients, to the development of the knowledge-based economy, and economic growth.

Prof. Hubert E. Blum, President, Federation of European Academies of Medicine (FEAM) and Dean of Medicine, University of Freiburg presented the views of clinical researchers focusing on the value of medical research and the need for transparency and consistency in the regulation of clinical research in the EU. He emphasised that clinical research is vital for Europe's economy (making reference to the UK Academy of Medical Sciences study which finds up to 40% annual rate of return on public investment in cardiovascular and mental health research) and that administrative burden can be reduced. Taking the example of complex research into personalised medicine, he advocated for urgent reforms of the current clinical trials authorisation process which should become clearer, simpler and streamlined. He concluded mentioning that all discussions about potential options for an improved regulatory framework should involve parties interested in research: patients, academia, industry and all other potential sponsors.

Answering a question from Prof. Juvin about how a new directive could support academic clinical research, Prof. Blum answered that a risk-based approach to clinical trials should be introduced.

Dr. Hartmut Krafft, Chair, EU Heads of Medicines Agencies' Clinical Trials Facilitation Group (CTFG), Coordinator of the Voluntary Harmonisation Procedure and Head of the Clinical Trials Section, Paul-Ehrlich Institute, Germany presented key figures about the Voluntary Harmonisation Procedure (VHP). Introduced in March 2009, the use of the VHP grew significantly from 15 submissions in 2009 to 84 in 2011 involving a total of 68 sponsors. Between 2009 and 2011, 100 positive opinions were adopted, against 5 negative. On average 6 Member States are involved in the discussions. The main features include:

- ✓ A set of electronic documents sent to one address (concept of *one stop shop*);
- ✓ Only general documents are required, which are part of any clinical trial application (Protocol, Investigators Brochure, Investigational Medicinal Product Dossier);
- ✓ A reliable timeline of 60 days for Sponsors and Member States; and
- ✓ Harmonised scientific discussion resulting in harmonised applications in the Member States.

Dr Krafft supported the need for simplification of the authorisation process of multinational clinical trials while maintaining the responsibility of Member States to authorise a clinical trial. He proposed that a legal basis should be developed for the VHP (concluding in a Coordinated Assessment Procedure?) and for the CTFG. He, however, stressed that IT challenges for the single portal and for the procedural steps of CTA approvals would need to be carefully thought through.

Dr. Krafft concluded that legislation and guidance on the process for authorising clinical trials will not solve all issues and that the future framework should be sufficiently flexible to allow for case-by-case decisions.

Prof. Olivier Chassany, Chairman of a French Ethics Committee, Paris, and Medical Head of the Department of Clinical Research and Development, AP-HP (Assistance Publique – Hôpitaux de Paris) focused his intervention on a risk-based approach to clinical trials, stressing that the current framework is a one-size-fits all regulation and that it is not adapted to the risks/constraints added by the research. He presented a classification of added-risks which is used since 2003 for tailoring the monitoring level by the institutional sponsor AP-HP for all their clinical trials (drugs, medical devices, surgery…). Such a classification for clinical trials of drugs has been recently adopted by UK [1] based on 3 levels from "no higher than the risk of standard medical care" (licensed drugs in their indications, dosage & form), to "somewhat higher than the risk of standard medical care" (licensed drugs used in a new indication) and "markedly higher than the risk of standard medical care" (Not licensed drugs, new drug under development). He emphasized that the best expert for setting at first the risk level added by a particular research is indeed the sponsor taking the responsibility for conducting the research. This risk level should be thereafter confirmed by the competent authority and/or by the Ethics Committee. The main issue is to reduce the current regulatory requirements for clinical trials at minimal added-risk for the patients, i.e. in which the drugs are given in usual care in their licensed indication. Indeed, these trials "in really life" setting are specifically promoted by institutional sponsors. It can be 1/ trials of comparative effectiveness (e.g. comparison of marketed drugs in plantar wart, influenza or malaria), 2/ or trials of optimization of therapeutic strategies such as the comparison of antibiotic duration in erysipelas or pneumonia [2]. Adapted requirements to such clinical trials at minimal risk could include: non-supply and alleged traceability of drugs, alleged notification of side effects, expedited review by Competent Authority, expedited Review by Ethics Committees. This last point is clearly highlighted by the US Code of Federal Regulations [3]. Such an expedited review is already applied by some European Ethics Committees [4]. He also mentioned the divergent roles and composition of Ethics Committees across the EU, and asked for a better harmonization of their ethical expertise which should be based primarily on the scientific benefits/risks & constraints ratio [5].

[1] MRC/DH/MHRA Joint Project: Risk-Adapted Approaches to the management of clinical trials of investigational Medicinal Products. October 2011

[2] Chastre J, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003; 290: 2588-98

[3] Code of Federal Regulations – Policy for Protection of Human Research Subjects: Expedited review procedures for certain kinds of research involving no more than minimal risks - 2009

[4] Wolzt M et al. Protocols in expedited review: tackling the workload of ethics committees. Intensive Care Med 2009; 35: 613-5

[5] Chassany O. Should European Independent Ethics Committees be dismantled? Intensive Care Med 2009; 35: 579-81.

Panel discussion moderated by Prof. Juvin:

The panel discussion focused mainly on two major issues: the definition of the risk-based approach to clinical trials and how to adapt the legislation accordingly, and the procedural aspects of a future Clinical Trials Authorisation.

On risk associated with clinical trials:
An important issue is the definition of risk, including the risk for patients participating in clinical trials (in terms of physical and mental integrity, and beyond safety, on data protection for example) and also for the data generated during the trial. One definition applying to all Members States would be difficult to achieve since the notion of risk is very subjective. Patients' input is necessary to assess the risks and benefits, and develop appropriate information for trial participants.

Nevertheless, Ethics Committees would favour an adaption of the burden of the clinical trials application process according to the risks associated with a trial.

On procedural aspects of a future Clinical Trials Authorisation:
Across Member States, there is no common division of responsibilities between National Competent Authorities and Ethics Committees. In France for example, the evaluation of the risk/benefits ratio is the responsibility of Ethics Committees, whereas in Germany it is the Competent Authority responsibility.

Patient knowledge should also be better used for the design, approval (particularly with their increased participation in Ethics Committees) and conduct of clinical trials. The new clinical trials legislation should ensure that barriers to patients' involvement – particularly at Ethics Committee level – are removed. Patients should be at the centre of the CTD revision.

The idea of a centralised procedure similar to the centralised marketing authorisation for medicinal products has a lot of limitations. The number of clinical trials applications per year is far higher than marketing authorisation applications (MAA) and their assessment would require a massive infrastructure. The timeline for assessing a MAA is about one year, which would be unacceptable for clinical trials applications. Conceptually, the applications are different since the MAA is usually based on a complete set of data looking at safety, quality and efficacy. A clinical trial application has a different scope.

Some stakeholders, particularly academics and patient groups, felt the CAP should be optional for single Member State trials but mandatory for multi-national trials.

A new legislative instrument could strengthen the legal base of the Voluntary Harmonisation Procedure and Clinical Trials Facilitation Group. While the CTD provided some benefits for the approval of clinical trials, there remain a lot of differences in its implementation across Member States. These differences can impact on clinical research. The key learning from the experience with the VHP is that there is no perfect system and that flexibility is needed.

Dr. Antonyia Parvanova, MD, MEP (Bulgaria, ALDE) wrapped up the event stressing that:

- A centralised procedure might not be in line with the vision of the Council of the European Union. "More EU is good", she stressed, but a centralised procedure is unlikely to receive approval and support from Member States, particularly regarding budgetary issues;
- A careful analysis of the loopholes created by the implementation of the CTD will need to be conducted and lessons will need to be learnt;
- The revision should prioritise:
    - Patients: clinical trials should be conducted in the best interest of patients;
    - Transparency: the process and stakeholder involvement should be sought;
    - A model of mutual recognition between Member States for clinical trials authorisations;
    - A risk-based approach adapted to the risk for patients and data associated with the trial; and

- The recognition of the specificities of some diseases areas – such as rare disease – in the design, approval and conduct of clinical trials.