

DIA EUROMEETING 2010 – March 8-10, Monaco From the Patient Fellowship “Report Team”

Now in its fifth year, the DIA Patient Fellowship is a programme aimed at promoting the active participation of Patient Organisations’ representatives. Developing a new volunteer action to enhance the role of patient representatives, we decided to ‘report on’ some key sessions at the 2010 DIA EuroMeeting by “patients’ experts”.

A “congress report team” was established to provide summaries of relevant sessions.

We convey our thanks to:

Britta Berglund, Rare Diseases Sweden

Vanessa Ferreira, AESCDG - Asociación Española del Síndrome de CDG, Spain

Greetje Goossens, European Myeloma Platform

Monika Nemanyte, Club 13 & Co. (association of people with mental disorders and their friends), Lithuania

Kathy Oliver, International Brain Tumour Alliance, UK

Fanny Vincent, Alliance Sanfilippo, France

Vlasta Zmazek, DEBRA (Epidermolysis Bullosa), Croatia

Gerard Nguyen, Rett Syndrome Europe, **Maria Mavris** and **Ariane Weinman** from Eurordis, acted as reviewers.

The opening plenary session paved the road for the rest of the conference. Regenerative, preventive, integrating, personalised and biomarkers are medicines of the future. “Bring them to patients” was the theme throughout the meeting. Drugs that are not actively being developed today are antibiotics, heart medication and drugs for psychological illnesses.

Questions that were raised were:

“Are the drugs good? Yes! Do the patients get these? No! Do we develop the right medicines? No!”

TABLE OF CONTENT

“Introduction to European Regulatory Affairs”	2
“Health Technology Assessment (HTA): Everything you ever wanted to know but were too afraid to ask!”	3
“Patient Influence on Regulatory Decisions: How much do they and should they have?”	4
“Patient use of information on medical products”	5
“How involved can informed patients be in the development and commercialisation of medicines?”	6
“Pharmaceutical Package: Information to patients’ proposals, what difference will they make?”. 7	
“Regulatory challenges and experience with new paediatric requirements” – with a focus on Orphan Medicinal Products	8
“Design and conduct of ethical paediatric clinical programmes”	8
“Harmonised regulatory expectations for juvenile animal testing?”	9

“Introduction to European Regulatory Affairs”

This DIA tutorial 17 provided an excellent overview of the European Union’s regulatory processes for obtaining marketing authorisation for medicinal products.

Professor Dr Rolf Bass (Pharmaceutical Business Consultant) - stepping in for the scheduled presenter Brenton James who unfortunately was unable to attend the DIA conference - gave a lively lecture on European regulatory affairs with plenty of time for delegate participation and questions.

Professor Bass first described the background to the creation of the European Union (EU) and the European Economic Area (EEA). Between 1957 and 2007, there have been six enlargements of the EU which today comprises 475 million people in 27 Member States (with 751 members of the European Parliament).

Professor Bass also described the structure of the European Commission which initiates community policy, manages those policies and negotiates international trade and cooperation.

The control of medicines in the EU is a complex topic supported by an EU legal framework for pharmaceuticals. Flowing out of the Commission come Regulations and Directives. For example, Directive 2004/27/EC relates to safety, efficacy, testing guidelines, etc. Regulation (EC) No 726/2004 lays down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMA).

There are three regulatory procedures available in the EU for obtaining marketing authorisation for medicinal products:

A **centralised EU procedure** for approval of medicines was agreed in November 2005.

The centralised procedure is handled by the European Medicines Agency (EMA) which oversees the CHMP (Committee on Human Medicinal Products) and the CVMP (Committee for Veterinary Medicinal Products).

The CHMP and CVMP review applications for products - looking at quality, safety and efficacy - and a rapporteur or co-rapporteurs are appointed to oversee these procedures. Decisions of the scientific committees of the CHMP and CVMP are then reported to the Commission.

For centralised procedures there are binding decisions which are signed by the European Commission. The centralised procedure is mandatory for practically all orphan drugs.

The centralised procedure usually takes six months, an average of about 170 days. Timetables are set according to the meeting schedule of CHMP and CVMP. The decision process takes up to 67 days and extra days have to be added for translation procedures, etc.

Mutual recognition procedures and decentralised procedures are two other methods for approving medicinal products.

The **Mutual Recognition (MR)** procedure is the process that allows for the harmonisation of product authorisations between European Union Member States (MS). So if a product has already been the subject of authorisation in one or more Member State/s, then this process can be a faster and less expensive way of gaining marketing approval.

The **decentralised procedure** for approval of medicinal products is less complex and is used for products which have not been authorised for use in an EU country via a Marketing Authorisation (MA). This procedure is often used for generics. It involves one or more Member States reviewing an application for approval.

Normally, there are about 50-100 applications annually for centralised procedures and about 1,000 for decentralised procedures.

It was interesting to learn that medical devices have no centralised approval agency in Europe and are regulated in a different way. Sometimes there is a product which is a combination of a device and medicinal product. For medicines there is Marketing Authorisation (MA) as mentioned above. For devices there is Certification which is called the “CE” mark.

It is important to remember that Marketing Authorisation for medicinal products is no guarantee of a patient being able to access a therapy on a national health service reimbursable basis in his or her own country. Increasing use of “health technology assessment” (HTA) organisations which consider the cost effectiveness of a therapy after Marketing Authorisation is granted may mean that a medicinal product – despite being granted an MA – is still beyond the reach of a patient if that medicine is considered not cost effective enough by the HTA.

Kathy Oliver

“Health Technology Assessment (HTA): Everything you ever wanted to know but were too afraid to ask!”

Tutorial 21 aimed at providing an overview on concepts and techniques involved in global HTA. Dr. Kym Alnwick (Heron Evidence Development, UK) chaired the tutorial session and talked about the objectives. She wanted to provide a solid basis of major aspects of HTA. She defined how healthcare technology and technology assessment are merged and the differences between appraisal and assessment. The global context of HTA, its development and the roles of different agencies in some countries were described. Various aspects of HTA include innovation, new drugs, end-of-life treatments and Orphan Drugs as well as ethical decisions.

Different concerns from patients and industry were illustrated. The decisions to market a drug have an impact and raise questions such as who will pay for the drug?

There exist different systems: Horizon Scanning systems aiming to identify, filter and prioritise new and emerging health technologies to assess or predict their impact on health and costs to society. There are different scales used to compare effectiveness such as the **Jadad scale** (Clinical Trial Quality score), risk-ratio, mixed treatment.

In the UK, the HTA is based on the analysis of the **QALY** and the **ICER**. **QALY** is a measure of disease burden, including both the quality and the quantity of the life lived. The quality of life is a measurement of components such as: mobility, anxiety/depression, pain, independence, activities of daily living. **ICER** (Incremental Cost-Effectiveness Ratio) is the ratio of the difference in costs versus effects. New drugs are typically funded if ICER is below cost/QALY of £20,000. For example, NICE (UK National Institute for Health and Clinical Excellence) guidance on the use of the “X” drugs in the NHS (UK National Health Service) can conclude that “X” drugs would be costly to the NHS without clear benefit.

HTA requires expertise from various disciplines. Sometimes, HTA methods differ across agencies and they can have different impacts on the assessment. The resources and health budgets are limited and the agencies have to consider many different factors: clinical, legal, economic, social and ethical. There are many controversial dilemmas to be resolved. For example: should the NHS spend the same amount of money to save or improve the quality of life of a 75 year-old smoker as it would for a 5 year-old child? Dr. Alnwick proposed an even more complicated dilemma by taking out the word “smoker”. After consulting a citizen group, NICE decided that the NHS should spend the same amount of money.

Some treatments can save lives but it would not be recommended by an HTA because of insufficient clinical evidence or uncommon use.

It can be concluded from this tutorial that it seems difficult or even impossible to conduct an assessment in the field of Health Technology without the direct or indirect involvement of a

diverse range of different expertise: health care professionals, researchers, politicians, decision-makers, patients (their organisations and interest groups).

The EUnetHTA collaboration encompasses 25 founding partners in Europe and gives a proposal for sustainable permanent collaboration for HTA in Europe.

Britta Berglund and Monika NemanYTE

“Patient Influence on Regulatory Decisions: How much do they and should they have?”

Nowadays, the research is taking into account the patients' needs and their organisations provide input concerning different aspects such as the quality, safety and benefit of some therapy or medicaments. Moreover, the regulatory measures should be focused on what the patient *needs* to know, instead of what it would be nice to know.

Vanessa Ferreira

Alastair Kent talked about the Genetic Interest Group in the UK. He highlighted the patients' inputs in these regulatory processes to raise important questions for patients. The quality of applications is improved since patients have been involved and today, patients are represented in different groups. He said that the future holds personalised medicine in healthcare, and this was mentioned in the plenary session. Jeremiah Mwangi then presented the International Alliance of Patients' Organizations (IAPO), which encourages participation, provides support and education to patient representatives and monitors what makes a difference.

Britta Berglund

Patient Organisations' contribution to EMA policies

Patrick Salmon (CHMP, European Medicines Agency (EMA), Senior Medical Assessor, Irish Medicines Board) focused on the experience and the perspectives of patient organisations contribution to EMA policies.

Health care policy should ideally reflect a right balance between regulatory decisions and the patients' choice or even better: the regulatory decisions should reflect the patients' choice.

This was certainly not the case in the past, where regulators in an ivory tower, far away from the reality of the patients' life, took care of the protection of public health. However, in the last decennia, there have been gradual changes in this *mysterious* approach of the regulators. This change in attitude was necessary because citizens in the modern world take a more active interest in healthcare issues and patients are increasingly eager to inform themselves about medicines and treatment options available. In this context, the EMA has committed to open the debate with its stakeholders and to increase the transparency of its activities. Consequently, a number of mechanisms have been created to involve patients in the activities of the Agency and in the decision making processes.

Some examples of patient involvement:

- Membership of the EMA Management Board
- Membership of three scientific Committees:
 - COMP (Committee for Orphan Medicinal Products)
 - PDCO (Paediatric Committee)
 - CAT (Committee for Advanced Therapies)
- PCWP (Patients' and Consumers' Working Party)
- Ad-Hoc participation in the activities of the CHMP
- Review of Product Information (EPAR summary and package leaflet)
- Membership of the Working Group on Clinical Trials in Third Countries
- Patients act as observers in the Pharmacovigilance Working Party (PhVWP)

For all stakeholders, the involvement of patients in the EMA activities proves to be a big success. With their expertise, patients and consumers of medicines have a unique and specific knowledge to offer and are therefore key stakeholders in the work of the Agency.

This fruitful collaboration, which has never delayed any of the EMA procedures, has much increased the transparency and has improved the regulatory outcomes.

In the future, the Agency will further broaden the collaboration with patients and particular focus will be on the patients' early input on the evaluation of medicines during the licensing processes.

This important topic has been included in the Agency's Roadmap 2015.

Greetje Goossens

“Patient use of information on medical products”

This was a very interesting session with several patient representatives attending.

The European Patients' Forum (EPF) was presented by Anders Olauson. EPF consists of 42 federations of patient organisations representing 150 million patients with chronic conditions, and it is their voice at the European level.

EPF is currently actively involved in European policies on information to patients on medical products. It strongly believes that: “All patients have a fundamental and legitimate human right of access to information about their health, medical conditions and the availability of treatments including knowledge of the best available management of their disease”.

Joana Gabriele talked about the Patients University Project in Spain. The aim is to guarantee equality in health learning and in access to high-quality care. The Academic Board of UP University, School of Medicine in Barcelona takes part of this project. It is a virtual class-room, centred in clinical conditions. This is a very interesting project that we will hear more about.

Other speakers - Tomasz Szelagowski, Federation of Polish Patients, and Nikos Dedes, AIDS treatment Group - addressed the lack of certified central services with full information on drugs. Only few manufacturers' internet sites contain information on characteristics of drugs. Some physicians are reluctant to provide full information on drugs and in addition, there is limited physician time for consultation with patients.

Suggested actions were a better recognition of the role of patient organisations and training of patient representatives when participating in drug information contexts.

Britta Berglund

“How involved can informed patients be in the development and commercialisation of medicines?”

This presentation was very understandable and close to “normal” life with lot of issues to be addressed. What is important is *the informed patient*, i.e. a patient who understands that he/she can make decisions or participate in decision-making processes. In order to achieve this, patients need more education/trainings.

A very good idea is “Patients College” – Dr. Mary Baker's project. In my opinion, for countries such as Croatia, this is an idea that could be implemented and developed.

Vlasta Zmazek

Regulatory bodies such as the European Medicines Agency (EMA) are now anxious to involve patients more in their work.

Isabelle Moulon, Head of Medical Information at the EMA, gave a very interesting presentation on the “Added value of involving patients: the experience of the European Medicines Agency”. The EMA involves patients in many aspects of their work (including patients serving on the management board of the EMA and on three committees), recognising that patients should be pro-active in this area. Dr. Moulon said it will be important to also involve patients more formally in discussions on benefit/risk assessment of new products. Another important area to involve patients in is pharmacovigilance, i.e. in safety communications about medicinal products. However, said Dr. Moulon, it is important that patient advocates be given training in understanding the regulatory environment and also that financial support to participate in the activities of the EMA be given to unpaid patient representatives and volunteers.

Other excellent speakers in this session included Sylvia Lyon, Director of Global Advocacy and Professional Relations, Endocrinology, Lilly, France and Mary Baker, MBE, President of the European Federation of Neurological Associations (EFNA).

Sylvia Lyon also called for more training programmes and involvement of patients in regulatory matters and also HTA (Health Technology Assessment). In summary, she said, there is an “increased need for informed patient input”.

Mary Baker emphasised the importance of remembering that “patients are not a species – they are you and I. There is no way off this planet without saying ‘I am a patient’”.

She touched not only on issues faced by patients but issues faced by caregivers as well. Very importantly, she said, it was crucial that patient groups – who often compete with each other in the same disease area – should work more collaboratively. “Partnership,” she said, “is the only way”.

Kathy Oliver

“Pharmaceutical Package: Information to patients’ proposals, what difference will they make?”

Today, there is an identified need for the guarantee of quality information published on drugs and maintaining patients’ trust.

Dr. Martin Terberger, Head of Unit Pharmaceuticals at the European Commission, pointed out that the issues currently at stake for a legal proposal on information to patients are:

“- no common rules on non-promotional information: divergent practices on the provision of information to patients across the EU;
- patients increasingly empowered and proactive users of healthcare: increased demand for information”.

The EU Parliament – ENVI Committee (Environment, Public Health and Food Safety) committee will hold an exchange of views on the information on medicinal products subject to medical prescription (amendment of regulation (EC) NO 726/2004 and amendment of Directive 2001/83/EC). The Rapporteur is Christofer Fjellner, PPE, Sweden.

The ENVI Committee is scheduled to issue a draft report in May 2010 to be discussed in June/July 2010 in the plenary session of the European Parliament.

The European Commission has some key items regarding a legal proposal on information to patients:

- Types of information to be disseminated;
- Channels for the dissemination of information;
- Quality criteria and conditions to be fulfilled;
- Specific rules on Internet websites;
- Monitoring and enforcement.

“Cumulative application of rules will allow workable distinction between advertising and information”.

During this DIA session, real added values were discussed such as evidence based, ICT (Information and Communication Technology) and information to patients, health literacy, patient-health professional communication skills.

Ms Nicola Bedlington, European Patients’ Forum, addressed several concerns such as the European “Code of Good Practice”, patient’s involvement on information to patients and banning Direct-to-consumer advertising (DTCA).

The *quality principles* on information to patients developed and endorsed by the European High-Level Pharmaceutical Forum are: Objective and unbiased, patient-oriented, evidence-based, up-to-date, reliable, understandable, accessible, transparent, relevant and consistent with Statutory Information.

Concerns and way forward for the patients’ involvement:

Current difficulties exist in clarifying the precise role of patient organisations’ involvement, finding suitable patients’ experts able to contribute to a specific activity and training consideration. The way forward is the revision of legal framework, involvement of observers in pharmacovigilance working parties, defining the role of patient/consumers in scientific committees, involvement of patients/consumers in benefit/risk evaluation and safety communication. In addition, it is important to provide an appropriate training to patients and financial support to attend meetings of scientific committees.

Britta Berglund

“Regulatory challenges and experience with new paediatric requirements” – with a focus on Orphan Medicinal Products

The aim of this session was to give an overview of the paediatric requirements and experience of the EMA Paediatric Committee (PDCO) three years after its creation.

Dr Daniel Brasseur, Chair of the PDCO, described the activity of this committee, the number of Paediatric Investigation Plan (PIP), waivers applications, the questions to be solved and the tools they use to improve the regulation.

The PDCO is responsible for the assessments and agreement of PIPs and waivers. Between 2007 and 2010, 668 validated applications were reviewed and among them only 19 received a negative opinion. The four questions that PDCO address are: has the candidate drug a place in paediatrics, for which condition, in which age group and implying a specific dosing drug.

Marketing authorisation applications for new products have to include the results of studies conducted in the paediatric population, in compliance with an agreed PIP.

Orphan medicinal products (OMP) are subject to the same requirements. The speakers provided the vision from a small and medium enterprise (SME) and the issues for developing an OMP. They described that most of OMP developments are from SME applicants and explained the sources of difficulties for a SME to respect the paediatric regulation. Developing OMPs are more difficult for a SME than for a big pharma company. Designing and performing clinical studies in an orphan indication is very challenging and even more in children and deviates from classical drug development. A question often raised by the speakers regarding the PIP is when to start the PIP submission and this remains under discussion. They generally agree that for some products (particularly for Advanced Therapy Medicinal Products) a discussion with the agencies is advised.

Learning points from their experiences are that you should evaluate and identify the right time for PIP submission in your OMP development, contact EMA-PDCO, SME office for scientific advice. Due to the early establishment of the paediatric regulation, sponsors and regulatory agencies are on the progressing learning curve.

Fanny Vincent

“Design and conduct of ethical paediatric clinical programmes”

Studying paediatric medicines implies doing clinical research with children. The objectives of the Paediatric regulation are to improve the health of children, increase high quality of care, ensure that paediatric studies are performed in an ethical way, increase availability of authorised medicines for children, increase information on paediatric medicines, achieve the above – without unnecessary studies in children.

The session provided an overview of the main questions regarding ethical aspects in paediatric research as consent and assent, blood volume, vulnerable population (neonates), adolescents, ethics committees, placebo, risk. For example, the information process provided to the child and the child's response should be clearly defined in advance and documented in protocols. Methods to improve the participation of children in the information and assent processes should be developed (separate information and assent sheets in language and wording appropriate to age, psychological and intellectual maturity).

A global initiative, STaR Child Health (Standards for Research with Children) was presented. The first meeting was held in October 2009. The goal of this international group of motivated and informed methodologists, child health care providers and decision makers is to assess current guidelines on paediatric research, identify the gaps in order to improve scientific standards for research and to ensure that evidence based standards are developed and utilised.

Fanny Vincent

“Harmonised regulatory expectations for juvenile animal testing?”

This session provided an overview of the regulation on juvenile animal testing in the context of (EC) No 1901/2006, the practical implications, and ten years of experience.

A comparison of the EMA and FDA guidelines was made. Similarities and differences were exposed. To sum up, several guidelines applicable to juvenile toxicity testing exist. The differences between EMA and FDA are relating to the need, the number of species and the dose selection. There is a need to define whether juvenile animal studies are required, to define which juvenile animal studies should be performed. The rat is a generally applicable species. When in doubt, it is advised to talk to the regulatory authorities.

An analysis of ten years of experience of centralised procedure and Paediatric Investigations Plans (PIP) was presented (number of juvenile animal studies in PIP, number of species used,...). Juvenile animal studies planned and performed in EU environment have clearly being considered after Paediatric Regulation establishment for different possible reasons (existence of appropriate guideline, need to include children earlier in the development plans of new medicines).

Fanny Vincent