

5 NEW TREATMENTS AND ORPHAN DRUG DEVELOPMENT

The European policy for Orphan drugs is one of the most successful policies of the European Union. This session presented a brief status report as of 2007 and challenges identified by the Committee for Orphan Medicinal Products (COMP) for its 3rd mandate 2006-2009. One hurdle is unequal access to orphan drugs and the diverging national policies for health technology assessment. The outcomes of an important European workshop organised by the French National Health Agency was presented. The voice of the rare disease community will also be heard in the shaping of the future EU policy on advanced therapies – gene therapy and cell therapy.

5.1 EU and USA Shared Interests in Orphan Drugs

- Shared interest for defending the Spirit of our Acts and Regulations from Mischief
- Harmonising Operations

Joint FDA/EMA Application for Orphan Drug status : it took five years to create it, and is a powerful tool to demonstrate both agencies' good will to collaborate. Industry can now submit a designation application to Europe and to USA at the same time.

Conceptual Framework for Prevalence/Medical Rationale for designation

- Confronting post-designation barriers to full approval
- The Clinical trial for Orphan Drugs is special!
- Jointly re-examine what has stymied drugs designated but not approved
- Linking Patient Groups Internationally
- Tropical Disease Medicines are Orphans Too. These diseases are considered as rare under our rules, however they are a concern for a large part of the human population
- Global Outreach to other Orphan Drug Activities (Japan, Australia, etc).



S P E A K E R

“ Dr Timothy Côté,
Director, Office of
Orphan Products
Development, FDA

5.2 Seven years of orphan drugs policy : what's next ?



S P E A K E R

Dr Kerstin Westermark, Chair of the Committee for Orphan Medicinal Products (COMP) – European Medicines Agency (EMA)

Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients” But “the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions” As “some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product (...) would not be recovered by the expected sales” (from (EC) No 141/2000 and (EC) No 847/2000).

An orphan medicinal product should be for a life-threatening or chronically debilitating condition affecting no more than 5 in 10 000 individuals in the Community or that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment. No satisfactory method of should be authorised in the Community or, the medicinal product should be of significant benefit. The tasks of the COMP include : opinions on applications for orphan drug designation; advise to the Commission on orphan drug policy; assistance to the commission in liaising internationally on orphan drugs and with patient groups.

The EU Commission provides incentives for orphan designated drugs, e.g. market exclusivity for 10 years from the time of marketing authorisation, fees reduction for drug development and via the mandatory centralised procedure, access to all 27 EU member states. Extended incentives for Small and Medium-sized Enterprises are available post authorisation. Priority to EU research programs is given. The regulation also calls for national incentives for orphan designated drugs.

After 7 years of orphan drug policy, it is fair to conclude that the Orphan Drug regulation has been a success. Up to November 2007, 759 orphan drug designation (ODD) applications have been received, 523 of which have gained positive opinion by the COMP, whereas 12 had a negative opinion and 193 applications were withdrawn by the sponsor. So far, 42 new products have received market authorisation, 3 are in decision making by the EU Commission. Three applications had negative opinions and 22 applications were withdrawn. The predominant therapeutic areas corresponding to the designated orphan medicinal products are rare cancers (c :a 50%), whereas e.g. metabolic disorders amount to c :a 10%. More than half of the products designated are potentially for paediatric use.

→ WHAT'S NEXT ?

1. In drug development?

Currently there is a strong trend - from “one drug fits all” blockbuster model - towards targeted treatments solutions for patients with particular diseases. This concept concerns innovative medicines (around 1/5 of orphan drug designations), advanced therapies, targeted and personalised medicines where orphan drug development could act as models. Such a development would benefit not only from a close collaboration between different companies contributing in their specific areas but also from a close collaboration between academic researchers and industry - in order to make real progress.

Orphan designated medicinal products comprise several examples of advanced therapies, such as gene therapy products for hereditary diseases, e.g. Duchenne’s muscular dystrophy, SCID (Severe Combined Immunodeficiency) and for rare cancers, e.g. glioma and renal cell carcinoma. Cell therapies have received orphan designation, e.g. for the treatment of acute liver failure, and even tissue therapy - for epidermolysis bullosa.

2. In economic development?

According to the EU Commission report, the orphan drug regulation has resulted not only in more jobs in the EU, notably in SMEs but also in a marked increase in R&D expenditure.

3. In collaboration?

The first and very important steps have been taken to a collaboration between the EMEA and the FDA; parallel protocol assistance/scientific advice between the EMEA and the FDA is already in place; recently, the Common EMEA/FDA application form for orphan medicinal product designation, in order to simplify simultaneous ODD application. The potential for an extended transatlantic work in parallel will be explored, as will also the possibilities for global collaboration with e.g. Japan and Australia.

4. For the COMP?

The role of the COMP as a “meeting point”/“initiation site” for collaboration and development between stakeholders – industry, patients, health care professionals/academia - is steadily increasing. The role of COMP members – at the EMEA in e.g. Scientific Advice Working Party (SAWP); in the EU Commission Rare Disease Task Force; as advisors to the EU Commission (DG Enterprise/SANCO/Research) is becoming

more and more important - as well as their roles in the member states as “ambassadors” for rare diseases and orphan drugs.

→ **OPPORTUNITIES AND CHALLENGES**

The incentives under the regulation - market exclusivity, protocol assistance and access to Community research programs has made it possible also for small enterprises to develop new drugs and bring them to the market. In the EU only, the orphan regulation could benefit some 15 million people suffering from rare conditions. Moreover, since the designation criteria also allow for the designation/development of conditions prevalent in developing countries but rare in the EU, the impact of the orphan regulation could be even greater. Further, by learning from the rare, common conditions might benefit from orphan drug development. Thus, the impact of the regulation has far exceeded the expectations at the beginning of the COMP mandate in April 2000. The challenges are several : allowing for the necessary profitability to stimulate research in drug development to achieve even more and better orphan drugs - yet keeping costs at a level where the drugs can still be affordable and available to the patients.



*Annex document : Orphan Medicines authorised in the EU
as of 26/11/2007 (centralised procedure)*

Medicinal Product	MA Sponsor	Authorised Therapeutic Indication
Fabrazyme	Genzyme BV	Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (-galactosidase A deficiency).
Replagal	TKT Europe AS	Replagal is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (-galactosidase A deficiency).
Trisenox	Cell Therapeutics (UK) Ltd	TRISENOX is indicated for induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptoralpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy.
Tracleer (Bosentan)	Actellion	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms inpatients with grade III functional status. Efficacy has been shown in : Primary PAH PAH secondary to scleroderma without significant interstitial pulmonary disease

Tracleer (Bosentan)	Actelion	Treatment of new digital ulcers in patients with systematic sclerosis and active digital ulcers
Glivec	Novartis Europharm Limited	Glivec is also indicated for the treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
Glivec	Novartis Europharm Limited	Glivec is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome (bcrabl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. Glivec is also indicated for the treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
Glivec	Novartis Europharm Limited	Glivec is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
Glivec	Novartis Europharm Limited	Treatment of adult patients with unresectable recurrent and/or metastatic dermatofibrosarcoma protuberans
Glivec	Novartis Europharm Limited	Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) as monotherapy
Glivec	Novartis Europharm Limited	Treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR gene re-arrangement
Glivec	Novartis Europharm Limited	Treatment of adult patients with hypereosinophilic syndrome (HES) and chronic eosinophilic leukaemia (CEL)
Somavert (Pegvisomant)	Pharmacia Enterprises SA	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.
Zavesca (Miglustat)	Oxford GlycoSciences (UK) Ltd (transferred to Actelion)	Zavesca is indicated for the oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.
Carbaglu	Orphan Europe Sarl	Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.
Aldurazyme (Laronidase)	Genzyme Europe BV	Aldurazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPSI; a [alpha]-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease
Busilvex (Busulfan)	Pierre Fabre Medicament	Conditioning treatment prior to haematopoietic progenitor cell transplantation in adult patients.
Ventavis (Iloprost)	Schering AG	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.

Onsenal (Colecixib)	Pharmacia-Pfizer EEIG	Reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP) as an adjunction to surgery and further endoscopic surveillance.
Photobarr	Axcan Pharma International BV	Photodynamic therapy (PDT) with porfimer sodium is indicated for : Ablation of high grade dysplasia (HGD) in patients with Barrett's Oesophagus (BE)
Litak (Cladribine),B)	Lipomed GmbH	Treatment of hairy cell leukaemia
Lysodren (Mitotane)	Laboratoire HRA Pharma	Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of Lysodren on non-functional adrenal cortical carcinoma is not established.
Pedea (Ibuprofen),M	Orphan Europe SARL	Indicated to close a patent ductus arteriosus in preterm newborn infants
Wilzin	Orphan Europe SARL	Treatment of Wilson's disease
Xagrid (Anegrelide Hydrochloride)	Shire Pharmaceuticals Ltd	Reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.
Orfadin (Nitisinone)	Swedish Orphan Int.	Hereditary tyrosinemia type 1
Prialt® (Ziconotide)	Elan Pharma Int.	Ziconotide is indicated for the treatment of chronic pain requiring intrathecal (IT) analgesia in patients who fail to obtain adequate analgesia and/or suffer intolerable adverse events with systemic opioids
Xyrem (sodium oxybate)	UCB Pharma Ltd	Treatment of cataplexy in patients with narcolepsy.
Revatio (sildenafil citrate)	Pfizer limited	Treatment of pulmonary arterial hypertension. Revatio has been shown to improve exercise ability and to reduce mean pulmonary arterial pressure.
Naglazyme (N-acetylgalactos- amine 4-sulfatase,A)	BioMarin Europe	Naglazyme is indicated for long term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI; (N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux Lamy syndrome) to treat the clinical manifestations of the diseases.
Myozyme (recombinant human acid alpha-glucosidase)	Genzyme Europe	Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid alpha-glucosidase deficiency)
Evoltra (2-chloro-9- [2 deoxy-2-Fluoro- β-D-Arabinofuranosyl] adeniteL)	Bioenvision Ltd	Treatment of acute lymphoblastic and acute myeloid leukaemia
Nexavar (Sorafenib tosylate)	Bayer Healthcare AG	Treatment of advanced renal cell carcinoma

Sutent	Pfizer Limited	Treatment of gastrointestinal stromal tumour (GIST)
Sutent	Pfizer Limited	Treatment of advanced and/or metastatic renal cell carcinoma (MRCC)
Savene (Dexrazoxane)	Topo Target A/S	Treatment of anthracycline extravasation
Thelin (Sitaxentan sodium)	Encysive (UK)	Treatment of idiopathic pulmonary arterial hypertension (IPAH) or pulmonary arterial hypertension
Exjade	Novartis Europharm Limited	Treatment of chronic iron overload due to blood transfusions (transfusion haemosiderosis) in adult and paediatric patients (aged 2 years and over)
Sprycel (dasatinib)	Bristol-Myers Squibb Pharma	Treatment of chronic myeloid leukaemia (CML) and philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL)
Sprycel (dasatinib)	Bristol-Myers Squibb Pharma	Treatment of adults with chronic accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate
Inovelon (Rufinamide)	Esai Limited	Adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years and older
Diacomit (Stiripentol)	BIOCODEX	Treatment of severe myoclonic epilepsy in infancy
Elaprase (iduronate-2-sulfatase)	TKT UK	Treatment of Hunter syndrome (Mucopolysaccharidosis II)
Cystadane (betaine anhydrous A)	Ophan Europe	Treatment of homocystinuria
Revlimid	Celgene Europe Ltd	Treatment in combination with dexamethasone of multiple myeloma patients who have received at least one prior therapy
Soliris (Eculizumab)	Alexion Europe	Treatment of paroxysmal nocturnal hemoglobinuria (PNH)
Siklos (hydroxyurea)	Addmedica	Prevention of vaso-occlusive crises in patients with symptomatic Sickle Cell Syndrome
Increlex (Mecasermin)	Tercica Europe Ltd	Treatment of growth failure
Atriance (Nelarabine)	Glaxo Group Ltd	Treatment of T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)
Gliolan (5 aminolevulinic acid hydrochloride L)	Medac GmbH	Visualisation of malignant tissue during surgery for malignant glioma
Yondelis (Ecteinascidin 743 L)	PharmaMar SA	Treatment of advanced soft tissue sarcoma



*Annex document : Orphan Medicines authorised in the EU
as of 26/11/2007 (mutual recognition)*

Dudopa (Levodopa/Carbidopa)	NeoPharma	Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results	MUTUAL RECOGNITION PROCEDURE : Sweden Recognised by : Austria, Denmark, Finland, France, Germany, The Netherlands, Norway, Portugal, Spain
Impavido (Miltefosine, P)	Zentaris AG	Treatment of visceral leishmaniasis caused by <i>Leishmania donovani</i> after failure of standard therapy	MUTUAL RECOGNITION PROCEDURE : Germany

5.3 Preparing the European scenario for advanced therapies (gene therapy, cell therapy, future EU Regulation)



S P E A K E R

This presentation addressed :

Gene / cell therapy : emergence

- Orphan drug designation
- On-going clinical trials
- 1st MAA on going

Regulations on advanced therapies : update

Development and marketing on advanced therapies : Key issues, bottleneck, reflections to be addressed


→ GENE / CELL THERAPY : EMERGENCE AND ORPHAN DRUG DESIGNATION

To obtain the orphan drug designation, 5 to 7 months are necessary : an initial meeting at the European Medicines Agency (EMA), then 2 months to submit the file (disease information, proof of concept, 1st pre-clinical results), and finally the evaluation that can last for 3 to 5 months in the absence of questions.

When the orphan drug designation is granted, the product becomes a priority for regulatory agencies, the orphan designation receives 10 years of exclusivity in all Member States, protocol assistance at EMA,

Dr Anne-Marie Masquelier, Chief Executive Officer, Genethon, France

direct access to the centralised procedure for the assessment of the risk/benefit for marketing authorisation, and fee reduction for the centralised procedure.

 *The table below summarises advanced therapies that are designated as orphan :*

NPN	Indication	Prev /10000	Sponsor	Designation date
Cytochrome P450 isoform 2B1 gene transfected human embryonic kidney 293 cells encapsulated in polymeric cellulose sulphate	Treatment of pancreatic cancer in combination with ifosfamide	1	FSG BTnologie Austrianova GmbH	30/06/03
herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes	Adjunctive treatment in haematopoietic cell transplantation	0,2	MolMed SpA	20/10/03
HLA-A2 restricted CD8 ⁺ T-cell line expressing MART-1 T-cell receptor	Treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients	3,6	CellC ApS	21/06/04
human autologous mesenchymal adult stem cells extracted from adipose tissue	Treatment of anal fistula	1,8	Cellerix SL-CSIC	26/08/05
human heterologous liver cells	Treatment of acute liver failure	3,36	Cytonet GmbH & Co. KG	11/04/06
Autologous CD34 ⁺ cells transfected with retroviral vector containing the human gp91 (phox) gene	Treatment of chronic granulomatous disease	NA	Vision 7 GmbH	28/08/06
allogenic (human) tumor cells, transfected with MIDGE vectors for the expression of IL-7, GM-CSF, CD80 and CD154, in combination with dSLIM immunomodulators	Treatment of renal cell carcinoma	3,5	Mologen AG	23/10/06
L-asparaginase encapsulated in red blood cells	Treatment of acute lymphoblastic leukaemia	0,5	Erytech Pharma S.A.	27/10/06
ex-vivo cultured adult human mesenchymal stem cells	Treatment of acute graft-versus-host disease	1	Quintiles Ltd	20/02/07

NPN	Indication	Prev /10000	Sponsor	Designation date
autologous dendritic cells loaded with autologous brain tumour cell lysate	Treatment of glioma	1	Dorian Regulatory Affairs BV	15/02/07
autologous CD34+ cells transfected with lentiviral vector containing the human ARSA cDNA	Treatment of metachromatic leukodystrophy	NA	Fondazione Telethon	13/04/07
human heterologous liver cells	Treatment of ornithine-transcarbamylase deficiency	0,1	Cytonet GmbH & Co KG	14/09/07
retroviral gamma-c CANA containing vector	Treatment of Severe Combined Immunodeficiency (SCID)-XI Disease	0,003	Genopoietic S.A.S.	30/05/01
adenovirus-mediated herpes simplex virus-thymidine kinase gene	Treatment of high-grade glioma with subsequent use of ganciclovir sodium	0,7	Ark Therapeutics Ltd	06/02/02
recombinant adenovirus carrying a gene coding for the human interferon gamma	Treatment of cutaneous T-cell lymphoma	0,63	Transgene S.A.	09/07/03
herpes simplex virus lacking infected cell protein 34.5	Treatment of glioma	0,8	Crusade Laboratories Ltd	09/07/03
adeno-associated viral vector expressing lipoprotein lipase	Treatment of lipoprotein lipase deficiency	0,02	Dr. Aart Brouwer	08/03/04
vascular endothelial growth factor-D gene in an adenoviral vector for use with a collagen collar	Prevention of stenosis in synthetic grafts used in haemodialysis	0,4	ARK Therapeutics Ltd	08/06/04
adeno-associated viral (AAV) vector containing the human gamma-sarcoglycan gene	Treatment of gamma sacroglycanopathies	0,2	Généthon	21/10/04

NPN	Indication	Prev /10000	Sponsor	Designation date
adeno-associated viral vector containing modified U7 sn RNA gene	Treatment of Duchenne muscular dystrophy	0,5	Genethon	27/07/05
autologous CD34+ cells transfected with retroviral vector containing adenosine deaminase gene	Treatment of ADA-deficient SCID	NA	Fondazione Telethon	26/08/05

lentiviral vector containing the human Wiskott Aldrich syndrome gene	Treatment of wiskott aldrich syndrome	0,01	Genethon	24/01/06
adeno associated viral vector containing the human calpain 3 gene	Treatment of calpainopathy	0,1	Genethon	06/04/06
adenoviral vector containing human p53 gene	Treatment of Li Fraumeni Syndrome	0,05	Gendux AB	23/10/06
recombinant adeno-associated viral vector expressing human alpha-1 antitrypsin gene	congenital alpha-1 antitrypsin deficiency	2,5	The Matthews Consultancy Ltd	20/03/07
recombinant modified vaccinia virus Ankara expressing human 5T4	Treatment of renal cell carcinoma	3,6	Oxford Biomedica Ltd	26/01/07
recombinant adeno-associated viral vector expressing human alpha-1 antitrypsin gene	Treatment of Pompe Disease	2,7	The Matthews Consultancy Ltd	09/07/07
bilayer engineered skin composed of keratinocytes from the patient (autologous) and fibroblasts from a donor (allogeneic) embedded in a plasma matrix	Treatment of epidermolysis bullosa	0,4	Cellerix SL	28/05/06

→ **CLINICAL RESEARCH : CLINICAL TRIALS IN PROGRESS, TOWARDS MARKETING AUTHORISATION APPLICATION**

GENE THERAPY CLINICAL TRIALS	
Phase III (updated 11/2007)	22 enrolling (out of 32) Monogenic diseases : 0
Phase II/III (updated 11/2007)	6 enrolling (out of 13) Monogenic diseases : 0
Phase II TG (updated 11/2007)	95 enrolling (out of 169) Monogenic diseases : 1
Phase I/II (updated 11/2007)	131 enrolling (out of 258) Monogenic diseases : 12
Phase I (updated 11/2007)	473 enrolling (out of 801) Monogenic diseases : 31
Total of enrolling trials	727

→ **REGULATIONS ON ADVANCED THERAPIES : UPDATE**

Advanced therapies are medicinal products based on genes, cells, and tissues : tissue engineering, cell therapy, and gene therapy, as opposed to products based on biotechnologies and chemical products.

The European regulation for advanced therapies responds to the market segmentation that undermined industrial development until recently. Patients' access to new treatments was therefore hindered. Public consultations in 2002, 2004, and 2005 revealed public expectations for clear European rules in this domain, and this was true for all stakeholders : the need for a specific, harmonised and coherent EU regulatory framework.

→ **COMMITTEE FOR ADVANCED THERAPY (CAT)**

With the Regulation, a new committee has been established at the EMEA, pooling Community expertise. This is a multidisciplinary group : biotechnology, medical devices, risk management, ethics

→ **SPECIFIC PROVISIONS FOR SMES :**

For Small and Medium-sized enterprises, the current legislation Reg EC N° 2049/2005 provides fee reduction and deferrals, handling of translations, general administrative assistance, workshops and training sessions. In addition, the legislation will also provide certification of quality and non-clinical data.

The Legislation on Advanced Therapies defines clear rules, smooth procedures and a European wide market. Particular attention is given to certain categories of stakeholders such as academic teams or SMEs. Detailed requirements and guidance also influence the implementation and its economic impact. The Legislation keeps the pace with new scientific developments.

→ **DEVELOPMENT AND MARKETING ON ADVANCED THERAPIES : KEY ISSUES, BOTTLENECK, REFLECTIONS TO BE ADDRESSED**

1. Development of Advanced Therapies

Special clinical investigation centres for Gene Therapy and Clinical Trials must be supported : very few exist in Europe (particularly for Gene Therapy), imposing on patients to travel when they want to participate in these trials, but difficulties due to the pathology, the lack of familial environment, or the cost are limiting factors.

Patients' registries need harmonisation, rapid patient enrolment, feedback to patients' organisations.

2. Regulation

A unique IMPD file (Investigational Medicinal Product Dossier for the centralised mutual recognition should be created and a same entity should evaluate the Clinical Trials Application and the New Drug Application.

SUSAR should be reported to EMEA only, and there should be no reporting duplication to national competent authorities. National Ethics Committees will address cultural differences within Member States.

Good Manufacturing Practices Production sites for clinical trials: very few exist in EU for Gene Therapy and Clinical Trials, and with limited capacities.

Funding is limited, and creative solutions are needed to increase the research capacity, associating Pharmaceutical industry, Biotech companies, National, European, Venture Capital, business angels, private equity partners.....

3. Compassionate use / Marketing Authorisation Application

The EMEA now has the possibility to give an opinion on Compassionate use (indication, eligible patients...). However compassionate use programmes have a cost, and the Legislation states that unauthorised products can not be charged for. Exceptions exist, and Member States have different compassionate use systems. As most advanced therapies are developed by SMEs or Academic teams, logistical issues and cost issues are obstacles to patients' access to compassionate use.

Information on treatments, clinical sites and on-going or planned clinical trials should be more transparent. Patients' representatives and industry initiatives should link together to improve information in this domain.

The reimbursement of marketed products varies across countries, and this creates inequity in access to treatment throughout Europe. Furthermore, the development and manufacturing costs of advanced therapies are likely to be substantial.

→ CONCLUSION

- EU Regulatory is coming > advanced therapies are really coming
- Objective to facilitate and harmonise EU rules for development and MAA
- Clear Objectives to get equity across countries to get access to treatment
- Main issues : harmonisation across MS, funds, different ways of reimbursement across MS

5.4 Timely and equitable access to orphan medicines across Member States – The European HAS Workshop November 2006, Paris



S P E A K E R

“ Dr François Meyer, Evaluation of Pharmaceutical Products, Haute Autorité de Santé, France

→ INTRODUCING A NEW DRUG IN THE EUROPEAN HEALTHCARE SYSTEMS

Even though all products evaluated through the European centralised procedure are authorised the same day in all Member States, they are not all actually placed on the market at the same time. The marketing authorisation is the first step, and then the introduction into national healthcare systems is the second step, under the responsibility of Member States for the pricing, reimbursement, financing and implementation.

The availability of medicinal products after the marketing authorisation has been granted is the result of a chain of actions : appraisal (of the therapeutic value), listing (on the reimbursement list), pricing (free pricing policy, regulated pricing schemes), financing (budget for the purchase of the product), and appropriate health care organisation (product available in hospitals only, restriction to specialised doctors or not...). These decisions are taken at the national level, and sometimes at the regional level.

→ HAUTE AUTORITÉ DE SANTÉ WORKSHOP, NOVEMBER 2006, PARIS

Orphan Drugs in the EU : Toward a Common Approach for a Fair and Sustainable Patient Access

The French agency in charge of health technology assessment organised this workshop in November 2006. All stakeholders were represented, except the pharmaceutical industry. Four working groups gathered to address the following themes :

- WG 1 The epidemiology of rare diseases to assess the needs, chaired by Dr Ségolène Aymé
- WG2 The assessment of the potential clinical benefit in the pre-marketing phase and of the real benefit after marketing authorisation
- WG3 The economic evaluation of OD
- WG4 The sustainability of the system

→ ECONOMIC EVALUATION

The group discussed the adequacy of the assessment methods for rare diseases and orphan drugs. A seminar with leading health economists to see how to best address some of these issues was proposed. For economic evaluation of orphan drugs, experts are debating ethical issues about the apparent opposition between collective choices and individual preferences.

Does rarity have an economic value, as opposed to severity? The criteria on which decisions are made should be made clear and publicly available, and discussed. Research into society's values with respect to rarity compared to severity has to be fostered, with a comparative analysis between Member States.

The issue of risk-sharing in research and pricing should be discussed more thoroughly: when uncertainty prevails, who should accept the financial risk? The health care system alone or the health care system sharing the responsibility with the patient? Or with the marketing authorisation holder in case the product is not as effective as initially thought at the time of assessment?

→ SUSTAINABILITY OF THE SYSTEM

The need to clarify key concepts such as “market exclusivity” and “significant benefit” was recognised by all participants. To be in the best position to foresee future health expenditures, health care systems need more transparency from the industry on medicines and their cost. The weight of failing developments in these costs should be addressed.

An informal network of national authorities in charge of orphan drug pricing could be created. Common sets of criteria could be adopted for the pricing negotiations, so that a European ex-factory reference price could be proposed.

Nevertheless, the decision making will remain at the national level due to market and organisation of care specificities: other elements such as taxes, distribution mode, volume, other products in portfolio of the marketing holder, etc. should be considered.

Greater public investment in research and risk sharing on development costs should be promoted to contribute to ensure long term sustainability of the system.

→ ASSESSMENT OF THE CLINICAL OR THERAPEUTIC VALUE OF MEDICINAL PRODUCTS

- Necessity to increase knowledge of the natural history of Rare Diseases, for example in the absence of a comparator in the trials (comparison with historic cases and untreated patients)
- Assessment of the therapeutic value and natural history of the disease should take place before the placing on the market, without delaying development
- Importance to improve the quality of data on the product, and clinical end points in clinical trials are needed. Surrogate markers can only be used for the appraisal of therapeutic value only if they relate to clinical endpoints.

- Randomised clinical trials are the reference, but alternative methods exist
- Improve cooperation in the field of Health Technology Assessment : towards common assessment of some Orphan Medicinal Products within existing networks. MEDEV

is an informal network that could play this role. Networking within HTA (EUnetHTA DG SANCO project) can be helpful.

- Importance to manage uncertainty with post marketing data collection

→ CONCLUSION OF THE WORKSHOP

Cooperation between EMEA (COMP-CHMP) and HTA agencies on the assessment of significant benefit, relative effectiveness, choice of endpoints for clinical trials, and pharmaco-epidemiological studies is greatly needed.

→ HTA IS PERFORMED WITHIN A GIVEN NATIONAL CONTEXT

FRANCE	ENGLAND
100% of drugs are evaluated before decision	Limited number of drugs evaluated, topic selection
Two step procedure : clinical value first assessed by HAS, then a different committee negotiates the price with the marketing authorisation holder	One step procedure (NICE)
HTA (performed by HAS) focused on clinical effectiveness. Price not (yet) taken into account.	Freedom of pricing
Price decided by Economic Committee after negotiation with the company, and based on the results of HAS' assessment.	Assessment/appraisal of the drug includes cost-effectiveness (based on the price decided by the company) Cost/QALY, threshold? (Quality Adjusted Life Years)
National Budget	Primary Care Trust

The EUnetHTA is organising a conference in France at the end of 2008. In parallel, a public Consultation on Future EUnetHTA Collaboration beyond 2009 is open.

More information is available at : EUnetHTA <http://www.eunethta.net/>