6 TREATMENT AND CARE

6.1 Targeting research to improve quality of life

Importance of making accurate, simpler and easier diagnostic

(Table, figure 17): for each of these rare diseases, the second column indicates prevalence, third column indicates the « old-time » diagnostic tool and the last column the availability of a DNA test to simplify and improve diagnosis. Old methods are usually invasive, and less sensitive.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Yesterday</th>
<th>Now: DNA test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>1/ 4 000</td>
<td>muscle biopsy</td>
<td>+</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1/ 2 500</td>
<td>sweat test</td>
<td>+</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>1/ 6 000</td>
<td>muscle biopsy</td>
<td>+</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1/ 5 000</td>
<td>liver biopsy</td>
<td>+</td>
</tr>
<tr>
<td>Fragile X</td>
<td>1/ 5 000</td>
<td>caryotype</td>
<td>+</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>1/ 5,000</td>
<td>muscle biopsy</td>
<td>+</td>
</tr>
<tr>
<td>Huntington</td>
<td>1/10,000</td>
<td>clinical presentation</td>
<td>+</td>
</tr>
<tr>
<td>Incontinentia Pigmenti</td>
<td>1/10,000</td>
<td>skin biopsy</td>
<td>+</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>1/10,000</td>
<td>X-rays</td>
<td>+</td>
</tr>
</tbody>
</table>

The genetic heterogeneity that causes disorders is such that it is not always possible to predict the onset of a disease when the person is carrying a genetic predisposition.

Testing is not a research activity, it is part of the patient management, or of the carrier management when the parent is carrying a gene without symptoms. Scientific knowledge serves to help patients or parents in making their decisions. It is part of the medical activity and should therefore be transferred and organised by clinical care settings, and not be confined in research ones only.

Therapeutic solutions that already exist for genetic diseases

Even though gene therapy has been emphasised in the recent years, and should still be regarded as a promising field, other solutions do exist. They mostly derive from the knowledge of the genome, but they are not gene therapy per se:

- Dietary management
- Vitamin responsive metabolic diseases
- Organ transplantsations / cell therapy
- Protein / drug engineering
- Enzyme therapies
- Gene therapy: the first steps ...
- Conventional pharmacology

→ DIETARY MANAGEMENT OF INBORN ERRORS OF METABOLISM

- Low protein diet: Phenylketonuria (PKU), hyperammonemias
- High cholesterol diet: Smith-Lemli-Opitz syndrome
- Mannose: CDG1b Congenital Disorders of Glycosylation (Phosphomannano isomerase deficiency)

Mannose, physiologically produced from fructose and glucose, can not be metabolised due to the absence of the Phosphomannano isomerase enzyme. Clinical manifestations include liver insufficiency, profuse diarrhea, hypoglycemia. Age at onset: 3 m-6 yrs. Oral mannose supplementation corrects the deficit as shown below:

<table>
<thead>
<tr>
<th>Mannose (µmol/l)</th>
<th>T0</th>
<th>2-month</th>
<th>5-month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
<th>Prevalence</th>
<th>Now: DNA test</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDG1b PMI deficiency</td>
<td>Manose diet (0.2 g/kg/day in CDG1b PMI deficiency) (figure 18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAT</td>
<td>&lt;10</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Factor XI</td>
<td>5%</td>
<td>46%</td>
<td>76%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

→ VITAMIN/COFACTOR/SUBSTRATE RESPONSIVE METABOLIC DISEASES

- biotin (B8) .......... responsive carboxylase deficiency
- pyridoxine (B6) .......... responsive homocystinuria
- tocopherol (E) .......... responsive pseudo-Friedreich ataxia
- carnitine ............... responsive lipid myopathy / cardiomyopathy
• creatine ……………... responsive mental retardation. Arginine no longer metabolised into creatine, thus provoking muscle and brain abnormalities. Treatment based on creatine monohydrate (1mg/kg/), arginine-contrôled diet and high ornithine diet successfully improve the condition (no extra-pyramidal syndrome, improvement of epilepsy, cognitive impairment improvement)

→ ORGAN TRANSPLANTATION / NEO-ORGANES / CELL THERAPY
• Kidney ……………… Polycystic kidney disease (PKD), nephronophthisis, Alport
• Liver ……………… a1AntiTrypsine deficiency, biliary atresia, metabolic diseases
• Heart ……………… obstructive cardio-myopathy, energy deficiency
• Bone marrow ……… Severe Combined Immune Deficiency syndrome, storage diseases
• CNS ……………….. brain « pace-maker »

→ PROTEIN/DRUG ENGINEERING
• Haemophilia: ………….. Factor VIII
• Diabetes mellitus: ……… Insuline
• Growth retardation: ………….. Growth Hormone
• Congenital adrenal hyperplasia: ………….. Steroids

→ ENZYME THERAPY (GENZYME, TKT)
• Fabry disease
• Hurler disease
• Gaucher disease
• Pompe disease

→ GENE THERAPY, THE FIRST STEPS ...
• A gap between promises and results
• A number of unsolved technical problems
• A limited number of indications …….. Immune deficiencies: selective advantage
................................................................................... Retinal dystrophies: tissue specificity
................................................................................... Inborn errors of metabolism
• A difficult approach: ………………… Toxicity (adenovirus, OTC, USA)
……………… Insertional mutagenesis (retrovirus, SCID, Paris)

→ CONVENTIONAL PHARMACOLOGY
• To rectify splicing: …………… Spinal Muscular Atrophy, Duchenne
……………… Muscular Dystrophy: possibility to switch from a severe form (Duchenne dystrophy) to a less severe form (Becker dystrophy) using antisense oligotherapy
• To rectify translation: …………. Gentamycine (in some cases of cystic fibrosis)
• To re-express a foetal gene: ……… Benzotaile, cysteamine for Isovaleric Vcidemia
• To clear/chelate a toxic: ……… Benzoate, cysteamine for Isovaleric Vcidemia
• To lock a pathway: …………… NTBC (Type I Tyrosinemia)
• To activate a pathway: …………. Fibrates, colchicine
• To inhibit a function: ………….. Bisphosphonates (Osteogenesis Imperfecta)
• To replace a function: …………. Melatonine (Smith Magenis Syndrome): deletion on chromosome.17p11.2, with mental retardation, speech delay, automutilations, temper tantrum, hyperactivity and major sleep disturbance. As shown in figure x below, circadian cycle of melatonine production is reversed in affected children.
…………………………….. Treatment with melatonine reverses this cycle to normal, decrease the child’s anxiety and temper antrum symptoms.
• To protect a function: ………….. Idebenone (Friedreich Ataxia)
CONCLUSIONS

• Identifying the disease-causing gene/mutation is consistently mandatory neither for diagnosis, nor for treatment.

• One does not suffer from a mutation, but rather from its functional consequences.

• Identifying the disease-causing mechanism helps devising the most appropriate therapeutic strategies.

• Identifying the disease-causing mechanism occasionally brings about elegant and efficient therapeutic tricks.

• Yet, identifying the mutant genotype might soon become very helpful for devising « à la carte » molecular approaches (exon skipping, nonsense mutations ...).

• The challenge is to identify the diseases that are presently treatable.

• Fundings are necessary but not sufficient: « One cannot order a discovery » Lavoisier.

• Beware of promises, single thoughts and dogmatisms; A partly efficient drug is better than nothing… and one should not disregard any approach.

• No disease is rare for the one who is affected.

Melatonin cycle is impaired during Smith Magenis syndrome as shown in figure 18 below:

Biphasonates are useful to treat Osteogenesis Imperfecta (OI), as seen on figure 19 below:

6.2 A response to the needs of the clinical trial community

European Clinical Research Infrastructures Network (ECRIN)

Prof. Ohmann talked about the infrastructure which might be of enormous help for treating and diagnosing rare diseases. Other presentations focused on “cooperation, working together, and networking” and also on the need for more funding, for sharing resources and for optimisation. This is what ECRIN is about.

Ambitious goals, not specific to rare disease clinical research:

• To initiate and to support development of new diagnostic and therapeutic strategies.

• To ensure adequate evaluation of efficacy and safety of medical products, devices, surgical techniques, etc.

• To improve quality and efficiency of clinical research.

The main problems clinical research is facing are:

<table>
<thead>
<tr>
<th>problem</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>transparency</td>
<td>limited transparency about ongoing and finished clinical trials</td>
</tr>
</tbody>
</table>
| patient involvement and acceptance | deficits with respect to patient involvement in clinical trials  
                                  | still poor “trial culture” in the community                               |
| legal and regulatory conditions | harmonisation by EU Directives but divergent national implementations    |
| sponsoring/ funding            | administrative burden for investigator initiated trials                    |
| quality                        | GCP but no harmonized practice and quality management                       |
| specific problems for subpopulations | deficient education of study personnel                               |
|                                | rare diseases — orphan drugs, pandiatrics — off label/ off licence,         |
|                                | incapacitated adults — informed consent, etc.                               |
move towards public registration of trials (Journal editors, WHO, Cochrane)

increased patient-orientation of clinical research

(Patient organisations, outcome research)

improved EU-framework conditions for specific populations (E.g. orphan drugs, paediatrics)

as a consequence of divergence in legislative systems:

• move towards public registration of trials (Journal editors, WHO, Cochrane)

• increased patient-orientation of clinical research

(Patient organisations, outcome research)

• improved EU-framework conditions for specific populations (E.g. orphan drugs, paediatrics)

some, but not enough initiatives for sponsoring/ funding of investigator initiated trials

• successful disease– specific networks conducting multinational clinical trials in the EU (e.g. EORTC)

But

• no systematic infrastructure to support multinational clinical trials in Europe

example: insurance in clinical trials

As a consequence of divergence in legislative systems:

• major differences regarding insurance of clinical research

(with respect to insurance coverage, type of sponsoring, drug approval status, type of trial, duration of insurance, etc.)

• extremely variable costs for insurance between countries

how ECRIN intends to solve some of the issues:

• bridge fragmented organisation of clinical research in Europe

• promote top harmonisation of support, training and practice for clinical research

• improve quality and efficiency of European clinical research

network structure

target of proposed actions

European Clinical Research Infrastructures Network (ECRIN)

-planned services of proposed concerted action

information and consulting (free)

• methodology, protocol review, adaptation of study protocol to transnational constraints

• ethical review

• meta-analysis

• centre selection, stimulation of patients enrolment

• cost evaluation

• funding opportunities

• biostatistics

• data safety and monitoring committees

• insurance

flexible integrated services (charged to the sponsor)

• interaction with ethics committees

• interaction with regulatory authorities

• drug dispensing

• adverse event reporting

• data management

• data monitoring

• management of biological samples (“biobanks”)
6.3 Treating with orphan drugs

Status Report and Health benefits after 5 years of Orphan Drug legislation

In her presentation, Melanie Carr, on behalf of Prof. Josep Torrent-Farnel, touched on the achievements of the orphan drug legislation, the protocol assistance, the marketing authorisations and the public health benefits to date.

The European orphan drug legislation consists of two regulations:


In April 2000, the EMEA received the first application for orphan medicinal product designation.

As provided for in the regulation, a review of the legislation is to take place after five years of orphan drug regulation. Therefore, the Committee for Orphan Medicinal Products COMP has prepared a report to the Commission, and this report will be posted on the EMEA web site.

The main recommendations that came out of this report are the basis of this presentation.

The aim of the orphan drug legislation is to address unmet medical needs of patients suffering from rare diseases within the Community, recognising that patients with a rare disease deserve the same access to treatment as all other patients. It is part of the Community policy to identify rare diseases as a priority area.

The legislation created incentives to attract the pharmaceutical industry and to develop interest on orphan drugs.

WHAT ARE THE EU INCENTIVES FOR ORPHAN DRUGS?

- Market Exclusivity for 10 years after granting of an EU marketing authorisation
- Centralised Procedure: direct access to EMEA
- Protocol Assistance: free scientific advice to optimise development
What kinds of products were designated? A majority were designated in oncology, and also for metabolic diseases, cardio-vascular and respiratory tract diseases to name but a few (see figure 21).

In terms of prevalence, 90% of designations are for conditions that are affecting less than 3 / 10 000 patients (see figure 22) which is far below the 5/10 000 cut off for the epidemiological definition of rare diseases (or 230 000 persons).

<table>
<thead>
<tr>
<th>Condition</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commission decisions</td>
<td>32%</td>
<td>36%</td>
<td>20%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>4%</td>
<td>4%</td>
<td>8%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Negative opinion</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Positive opinions</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Submitted</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

The COMP is responsible for:
- opinions on designation
- international co-operation
- advising on general EU policies

ACHIEVEMENTS: ORPHAN DESIGNATIONS

more than 480 submissions for designation (cumulated since 2000), of which 270 were designated.
The year 2004 was a record, with 108 submissions.
The year 2005 appears to be an active year as well, with 25 submissions in the last month (May 2005).
The Committee adopted its 300th opinion on designation during its meeting in May 2005.

Fee Reductions: reduction of centralised regulatory fees via special fund from EU budgetary authority (to date this represents 12 million euros)

EU-funded research grants from Community & Member State programmes
In terms of products, 21% of products submitted were biotech products. Innovativeness was also looked at, and the committee was pleased to note that 47% of products submitted were innovative ones; this includes novel chemicals, products for gene therapy and cell therapy.

Protocol Assistance is essentially Scientific Advice for companies developing Orphan Medicinal Products. It is particularly important for small and medium enterprises because it gives access to regulatory and scientific experts, thus a possibility for sponsors to discuss with them at an early stage.

In the majority of cases, protocol assistance gives the opportunity for oral explanation where additional and specific expertise (medical/patients) can participate. The COMP has recommended Protocol Assistance for more than 50% of designated OMP. For orphan drugs, the fee reduction is important (currently 100% = free). This financial effort will need to be sustained in the years to come.

As of May 2005, 99 dossiers for protocol assistance had been received. In half of the cases (50%), assistance was asked for clinical aspects of the development, 34% for the non-clinical, 11% for biotechnologies and 5% for quality areas.

Orphan Marketing Authorisations

Up to April 2005, 20 centralised marketing authorisations had been granted to date:

- Fabrazyme for Fabry disease
- Replagal for Fabry disease
- Glivec for chronic myeloid leukaemia
- Tracleer for pulmonary arterial hypertension
- Trisenox for acute promyelocytic leukaemia
- Somavert for acromegaly
- Zavesca for Gaucher disease
- Carbaglu for hyperammonaemia
- Aldurazyme for Mucopolysaccharidosis
- Busilvex for haematopoietic progenitor cell transplantation
- Ventavis for pulmonary arterial hypertension
- Onsenal for Familial Adenomatous Polyposis
- Litak for Hairy cell leukaemia
- Lysodren for adrenal cortical carcinoma
- Pedea for Patent Ductus Arteriosus
- Photobarr for Barrett’s oesophagus
- Wilzin for Wilson’s disease
- Xagrid for Thrombocythaemia
- Orfadin for Hereditary tyrosinemia type 1
- Prialt for chronic pain requiring intraspinal analgesia

Three extensions of indication were authorised (Glivec for gastrointestinal stroma tumor GIST, for first line use in Chronic Myeloid Leukemia CML, for paediatric use in CML).

Fifteen centralised applications are currently in the review process, and two marketing authorisations were granted through Mutual Recognition.

So the total of authorisations is 22.

Public Health Benefits

1. 22 orphan medicinal products have been authorised

The public health benefits of the EU orphan drug regulation are not easy to evaluate as they concern different areas. In terms of survival, life expectancy and quality of life it is too early to say what the impact has been on these parameters.

2. For the other designated products:

According to a recent EMEA survey of sponsors:

- 33% of orphan products are in final stage of clinical development (phase III)
- Up to 40% plan to file for marketing authorisation in the next 3 years
- Increased level of scientific and public awareness
- Creation of expert network (350 experts registered)
- International liaison with other Regulators, WHO, and NGOs on neglected diseases

Future Challenges Still Ahead

- Ensuring availability/access to OMP for all patients
- Affordability and long-term sustainability of the orphan drug initiative
- Sustained public funding from EU/national institutions
- Better epidemiological knowledge of many rare conditions
- Strengthen early pharmacovigilance planning and risk management strategies
- Promote National Incentives

Among Objective Benefits:

- Partnership with patient groups: the dialogue with patient groups had a positive impact on structuring network at EU level
- Impact on rare disease research
- Transparency & pro-active dialogue with interested parties
- Increased level of scientific and public awareness
- Creation of expert network (350 experts registered)
- International liaison with other Regulators, WHO, and NGOs on neglected diseases

Future Challenges Still Ahead

- Ensuring availability/access to OMP for all patients
- Affordability and long-term sustainability of the orphan drug initiative
- Sustained public funding from EU/national institutions
- Better epidemiological knowledge of many rare conditions
- Strengthen early pharmacovigilance planning and risk management strategies
- Promote National Incentives
CONCLUSION
As a final word, the true impact on public health has been in the figures: 270 designations, 45 applications for marketing authorisations, resulting into 22 marketing authorisations. From that, potentially more than 1,043,000 patients stand to benefit.

Promote Research into Rare Diseases
Academia has proven track record in “basic research”; it is able to move a concept hypothesis to the test tube, then to animal experimentation, but rarely to Human. Very few, if any, academic institutions in Europe can develop drugs. Academics can develop the science, the knowledge, but producing a drug is in the domain of the industry. Therefore partnerships between Academia and industry are vital:

- Academic (for the collection of biological samples, volunteer patients etc)
- Industry (drug development/ manufacture)

Something the Regulation has perfectly done is not to force, but to put academic groups and industry in the same room at the same time, to allow these collaborations to take place.

The academic networks are very strong and developed. Collaborative links exist, although in the rare disease community there is a sense that research centres are sparse. When only one or two centres exist that are interested by the same rare diseases, how much collaboration is going on between them?

Fortunately or unfortunately, academia is extremely competitive. “I want to be the first person identify that gene, not you!” Dr. Morland would argue that that is very healthy but other may consider this competition as a potential barrier to progress.

Research is not all about research and drug development, but it is also on epidemiology, diagnosis, prevention etc., domains where academic centres are leading the efforts.

Funding
Funding is the lifeblood of academic research. Unfortunately there is a bias towards “major diseases” provoked by the political dimension of research that drives research funding to cardiovascular disease, the elderly, mental health and cancer mainly. Research on rare diseases can be seen as an “orphan”. This is now changing.

EU funding is available: the pre-FP6 funding for rare diseases could fund a few research projects but on an “ad hoc” basis. Then the FP6 has specifically identified the need for research into rare diseases and this has to be applauded and congratulated. But we do not yet know whether FP6 has delivered for rare diseases. There has been a huge investment, but it will be some years before we know the results of the impact.
that investment in terms of scientific questions or benefits for patients. This will happen, but for the moment it is too early to say.

**FUTURE EU FUNDING, FP7**

There are very encouraging signs for FP7, as the COMP was successful in influencing the programme. Eurordis also produced a position paper on the subject, highlighting the following priorities:

- Descriptive and analytical epidemiology
- Genetic/molecular characterisation
- Pathophysiology
- Improving diagnostics
- Therapeutic research
- Research in human and social science
- Compliance with EU Directive on clinical trials
- Ethical submission
- Medicines “regulations”
- Local Investigational Review Board /R&D approval
- Human tissue act
- Data protection act

EU funding is important, but it contributes to only 5% to the total of the research budget available in the Community. The role of member states should not be neglected, as in addition to national research policies, member states are allowed to decide on national incentives for orphan drugs. They can vary considerably from country to country. However, the inventory of such incentives is not completed, it should be published and regularly updated, but data are difficult to collect. Again, partnership with industry is key to increase the research budgets. Some charities and patient organisations fund research too, but this is an exception, as in general they are small patient-driven.

**PROMOTING CLINICAL TRIALS IN RARE DISEASES**

How do you conduct effective clinical trials in rare diseases? We are talking about small patient numbers; we cannot use conventional scientific methodologies to study rare diseases. Some of these new methodologies with twenty patients still need to be validated and accepted by a wider scientific community and also regulatory authorities. For clinical trials, networks are also essential. In the cancer area, the situation can be seen as “luxurious” as very well established trial networks can conduct numerous trials. The fact that so many designations were obtained for anti-cancer drugs was not by chance, but thanks to these networks.

Funding is again becomes an issue for conducting clinical trials. EU Framework Programme has been very dominated by basic research not clinical trials, still trials are a vital part of bringing new treatments to patients and they need funding.

Industry struggles with rare diseases, finding the right collaborators or the correct number of collaborators that you need. It is a challenge to initiate lots of centres. We are now working in a “harmonised” clinical trials arena, and the promotion of clinical trials in that arena is not necessarily happening.

There are numbers of hurdles that academics have to face, and they are all for the right reasons:

- Compliance with EU Directive on clinical trials
- Ethical submission
- Medicines “regulations”
- Local Investigational Review Board /R&D approval
- Human tissue act
- Data protection act

There are pressures on everyone’s time, and in rare diseases clinicians have to go through the same bureaucratic processing for one or two patients than they would have to for five hundred patients with a frequent disease. This is a real dilemma, because the burden on putting these clinical trials together has to be eased for rare diseases.

**THE ORPHAN DRUG REGULATION**

It is definitely a huge progress for clinicians and patients. A large range of disorders now benefit from a treatment, even though a third are for cancer and two third for paediatric patients. For the other diseases, Dr. Morland questioned how to promote the orphan “orphans”? The products where little research is being made?

**CONCLUSIONS**

The Orphan Drug Regulation is bringing orphan drugs to patients. Whether or not the pace is quick enough is an open question. Often, the difficulty is to ensure that new discoveries are translated to treatment. This is an area where research incentives can make the difference: co-ordinated funding, promotion of trial networks. Reducing the bureaucratic burden for clinical trials is also a key solution. Finally, we must remember the Orphan Drug Regulation is not about academic prestige, it is not about profiting industry, it is about giving patients access to new, better, safer therapies.
Orphan Drug Regulation:
Views of a patient representative

In his introduction, Yann Le Cam insisted on the necessity to continue and to consolidate the work achieved so far thanks to the Orphan Drug Regulation that does not need to be changed after five years of adoption: it is working as only minor adjustments are needed.

Five Years of Successes: Main outcomes

- Increasing number and quality of orphan drug applications
- 300 positive opinions for orphan designation!
- For low-prevalence diseases, with innovative medicines, significant benefit over existing treatments, increasingly based on European research
- 22 marketing authorisations
- Benefiting potentially 1 million patients in Europe

During these five years, the pioneering role of patient representatives in the regulatory system, and the innovative dialogue with all interested parties has had a considerable input. A limit though, member states policies on orphan drugs are not as developed as expected and encouraged in the EU Orphan Drug legislation.

The participation of patient representatives as full COMP members and members of the COMP Working Group of Interested Parties is a major political step: patients are taking decisions as other experts, and the EMEA is the only drug agency where patients are playing this role. Other participation of patients in the regulatory process includes:

- Patient representatives as external experts for COMP or Protocol Assistance.
- Patient representatives as members of the EMEA/CHMP Working Group of Patient Organisations and of the EMEA Management Board.
- Patient representatives as future full members of the Committee for Paediatric Medicines and of the Committee for Advanced Therapies.
- Patient representatives to be consulted for the evaluation of Risk/Benefit ratio when assessing a marketing authorisation application, as well as on the patient information leaflet.

But beyond success, we need to recognize the lack of European and national overall policies on orphan drugs and call all interested parties and policy makers to join forces to address this loophole.

FIVE KEY ISSUES FOR THE FUTURE

→ 1st ISSUE: to develop more orphan drugs for unmet medical needs. Beyond the first 200 conditions that are now benefiting from an orphan drug, more diseases are left untreated.

Proposal:
- European & national policies for rare disease research (research priority, research agenda and funding)
- Progressive elaboration of an « Inventory of unmet medical needs » and regular « COMP Call for Interest » by therapeutic fields.

→ 2nd ISSUE: to improve the clinical development success rate to transform more orphan designated products into authorised medicines.

So far, from the 300 orphan designations, 22 orphan drugs are marketed. Comparing with the same flow in the US, where a fourth of designated products reach the market, is too early but we need to invent ways to improve this success rate in Europe. We must turn more orphan drugs “hopes” into “real” medicines.

Proposal:
- To create an « EU Orphan Drug Clinical Research Grant Programme » managed by EMEA / COMP through annual funds allocated by DG Research FP7. The office for Orphan Drugs at the FDA has a budget of 15 million dollars each year to initiate pre-clinical studies or Phase I/II studies. Europe could adopt a similar approach.

→ 3rd ISSUE: to promote patient access to orphan drugs in each Member State. We cannot accept that some drugs are still not available in all member states two years after their marketing authorisation.

Proposals:
- To implement the Commission Communication July 2003 and make the information about approved orphan drugs widely available (availability of drugs in each member state, distribution channel in each country, i.e. hospital pharmacies or community pharmacies, number of patients treated)
To create a Working Group on Orphan Drug Availability at DG Enterprise with some volunteering Member States, COMP representatives and patient organisation representatives, to assess the Therapeutic Added Value and set a European reference price (catalogue) with the company. This would be a pilot. The industry often advocates that a unique price policy would be more adequate for Europe, so we give it a try.

4th issue: to settle the unfair debate on orphan drug pricing

Some pretend that orphan drugs are expensive, or even too expensive. What does “too expensive” mean exactly? Does this mean that not all patients deserve treatment? They are not worth it? What would a scientific assessment of the positive risk/benefit ratio mean if yet another stakeholder states that I am not worth the product as a patient? This debate is unfair and should be closed.

Prior to the centralised procedure, some 200 other orphan products were already authorised in the EU, imported from the USA, and price was never an issue. Now that some are produced, developed, evaluated and marketed in Europe, with a return of investment in Europe and not in the USA, then the price should become an issue, all of a sudden? Europe playing against itself! Furthermore, orphan drugs authorised during the last five years are not more expensive than other innovative products marketed during the same period (cf. the Alcimed report to European Commission).

5th issue: to adopt a more international approach to designation, protocol assistance, marketing authorisation assessment and drug availability to patients.

Clinical development of orphan drugs is global. However expert centres, patients, financial resources are scarce. Time is a life and death issue. Issues raised by regulators in the US and EU are or should be the same, both for clinical development and post-marketing studies.

Proposal:
• To pro-actively propose parallel Protocol Assistance EMEA/FDA for orphan drugs when already designated on both sides
• To explore and implement possible parallel procedure for orphan medicinal product designation applications

Orphan Drug Regulation: Views of an industry representative

As a representative of EuropaBio and Emerging BioPharmaceutical Enterprises EBE, association of drug manufacturers that are developing the vast majority of orphan products in Europe today, Catarina Edfjall stressed that it is too soon to judge results of the Orphan Drug Regulation - but the outlook is promising and the pharmaceutical industry as a whole should support this Regulation. This position has been summarised in the Industry White Paper.

The industry analysis concludes that rare diseases are now identified as a priority area for community action within the framework of public health in Europe. However, it seems that member states need to better understand the spirit of the Regulation and adopt a more active policy on national incentives. Alcimed’s study confirmed that the price for an OMP in the EU is related to disease rarity and health systems. However, the Regulation does not concentrate on research programmes or on access. In the EU, only limited action has been taken so far to stimulate the development of Orphan Medicinal Products (OMPs). The experience in the USA and Japan show that the strongest incentive for industry to invest in development and marketing of orphan drugs is where there is a prospect of obtaining market exclusivity.

To improve the Regulation, the industry is making 9 recommendations (see the Industry White Paper):
1. Undertake an educational programme to build awareness about rare diseases in Europe, at the European level as well as the national level.
2. Establish an EU-wide network for diagnostic testing for rare diseases → timely intervention for patients.
3. Promote a Europe-wide compassionate use system for the provision of orphan medicines to patients.
4. Increase the understanding of the Regulation in MS and eliminate conflicts in national legislation.
5. Review the incentives for OMP development in the Member States (Article 9).
6. Eliminate the confusion around the 10-year market exclusivity (Article 8(2)) & correct translations.
7. Review disincentives to orphan drug development at the national level, e.g. additional requirements for clinical and cost-effectiveness data.
8. Facilitate clinical trials in the field of rare diseases, under the EU “Clinical Trials Directive,” & review cost implications of post-marketing commitments.
9. Coordinate and streamline EU rare disease research and therapy development within the Commission and with the EMEA and the FDA.

This should be worked on and implemented by the Commission in a spirit of collaboration with all stakeholders.

About the 6th recommendation, Catarina Edfjall explained that market exclusivity is the strongest EU Regulation incentive and that it should be protected.

According to her, the review of market exclusivity should only be based on the designation criteria.

The risk is that confusion about the application of market exclusivity could erode the incentive. To her opinion, market exclusivity does not lead to higher prices, but the rarity of the disease does.

As shown on figure x, market exclusivity provides no monopoly: for pulmonary arterial hypertension, many therapeutic options exist, some with an orphan drug status. Finally, market exclusivity provides partial exclusivity in respect of similar products: similar and competitor products need to be clinically superior.

Orphan Regulation has NOT created monopolies - example PAH

Approved products for treatment of PAH
- Ca-channel blockers oral
- epoprostenol prostacycline i.v.

Approved orphan products for treatment of PAH
- bosentan ERA oral
- iloprost prostacycline i.n.
- (sildenafil (US) PDE-5 oral)
- (Treprostinil (F) prostacycline i.n.)

Designated orphan products for treatment of PAH
- sitaxentan ERA oral
- ambrisentan ERA oral
- tadalafil PDE-5 oral
- vardenafil PDE-5 oral

An important question is whether market exclusivity protects the innovator doing pioneering research.

- Orphan Regulation should stimulate development of new medicines for patients without treatment
- First step: Research of a new therapeutic field requiring ‘pioneering’ work (new animal models, not yet validated endpoints, unknown safety profile…)
- Needs to be stimulated and rewarded
- Requires high investment and risk-taking
- So, in this context, is Market Exclusivity a real incentive?

CONCLUSIONS
Regulation should be continued and not be changed at this time.
Regulation should be more fully applied in member states, especially for Incentives and Access.
Avoid confusion about incentives, especially Market Exclusivity.
The field of rare diseases should be taken very seriously, it leads into personalised medicine.

Availability of orphan medicinal products in Europe

The review of real patient access to orphan drugs after their marketing authorisation has been granted by the Commission, is the objective of a regular survey conducted by Eurordis.

Only a part of a disease population has access to an orphan product, when existing: the disease population is represented by the prevalence, but in fact not all cases are diagnosed. And even among diagnosed cases, not all patients correspond to the treatment indication (for example children when only an adult formulation is marketed with no information on the dosage for children). Then another limitation resides in the contra-indications, e.g. liver function or renal function impairment.

Then, even for the patients who should be treated, an important obstacle is the delay in placing an authorised product on the market.

This delay can be explained (but in no way justified) by several factors:

- The delay for fixing the price (negotiations between marketing authorisation holder and member states’ authorities).
- The delay for deciding the reimbursement (for designated orphan products, the potential significant benefit is assessed at the time of designation by the COMP, at the time of marketing authorisation based on the marketing applications, the COMP assesses if the significant benefit still holds. So the therapeutic added value should automatically lead to reimbursement in each member state/EEE).
- The treating physicians’ lack of experience concerning the real medical benefits of these medicines and thus their reluctance to prescribe them. This can be the case
WHY MONITOR ORPHAN DRUG AVAILABILITY IN EU MEMBER STATES/ESEE?

Eurordis is entitled to monitor the drug availability as this is in the interest of patients and as the Council Directive 89/105/EC sets the delays for member states to place the products on the market after their authorisation:

- COUNCIL DIRECTIVE of 21/12/1988 - transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (89/105/EC)
- Article 2
  - 90 days legal delay to set a price which can be extended to 180 if questions arise

These delays are well known: already in the audit performed in 1999 on the performance of the EMEA and the European Regulatory System and such delays were registered for the first 96 products authorised through the centralised procedure (1995-1999).

They are shown in figure 24. By that time, the average delay was 190 days, exceeding the 180 legal days, with maximum delays of up to 708 days. For the rare disease community, the objective was to explore to which extent this was also the case for orphan drugs: if rare diseases are a priority, then logically the placing on the market should be rapid. On the contrary, in the absence of a public health priority for rare diseases, similar delays would be observed.

For these products, Eurordis asked several sources:

- IMS-Health, to detect sales in a sample of pharmacies in each member state (except Denmark)/EEE
- Patient organisations, to report on real availability of the products
- Marketing Authorisation Holders (MAH)
- National Competent Authorities

Eurordis RESULTS

Table 25 below presents the 12 first OMPs authorised prior to December 31st 2003 (starting 2000 for the very first orphan drugs marketed).

<table>
<thead>
<tr>
<th>Fabrazyme</th>
<th>Genzyme</th>
<th>Fabry Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replagal</td>
<td>TKT Europe</td>
<td>Fabry Disease</td>
</tr>
<tr>
<td>Trisenox</td>
<td>Cell Therapeutics</td>
<td>Acute promyelocytic leukemia</td>
</tr>
<tr>
<td>Tracleer</td>
<td>Actelion</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Glivec</td>
<td>Novartis</td>
<td>Chronic myeloid leukaemia</td>
</tr>
<tr>
<td>Somavert</td>
<td>Pharmacia</td>
<td>Gastrointestinal stromal tumors</td>
</tr>
<tr>
<td>Zavesca</td>
<td>Oxford Glycosciences/Actelion</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Carbaglu</td>
<td>Orphan Europe</td>
<td>N-acetylglutamate synthase deficiency</td>
</tr>
<tr>
<td>Aldurazyme</td>
<td>Genzyme</td>
<td>Mucopolysaccharidosis type 1</td>
</tr>
<tr>
<td>Bulsiwek</td>
<td>Pierre Fabre</td>
<td>Conditioning treatment prior to HPCT</td>
</tr>
<tr>
<td>Ventavis</td>
<td>Schering</td>
<td>Primary Pulmonary hypertension</td>
</tr>
<tr>
<td>Orimolel</td>
<td>Pharmacia Pfizer</td>
<td>Familial adenomatous polyposis</td>
</tr>
</tbody>
</table>

Participants at the conference
Data were collected until December 6th 2004; this was 341 days or 11 months and 6 days after December 31st 2003.

Figure 26 below shows the number of orphan products available in member states at the end of the data collection phase.

With the exception of Denmark, none of the member states had placed all 12 products on the market, one year or more after their marketing authorisation. The median number of products actually placed on the market is 5 out of the 12.

A first group of member states / EEE countries are doing better than average: Austria and France (11), Sweden (10), Finland, Germany and the Netherlands (9), then Italy, Spain and the United Kingdom (8). For a second group, only half or less of the authorised products are available: Ireland, Portugal, Norway, Belgium, Luxembourg, and Greece. The last group, mostly represented by member states that entered the community in 2004, 0 to 4 products only are available.

DISCUSSION

A first comment is the difficulty in obtaining the information about drug availability. Even though all possible sources were solicited, some data may be missing as each source had its limitations:

• Pharmacies’ sampling: the method may not be sensitive enough to capture orphan drug sales even when sample size is relatively large. For example only 3 hospitals are delivering Fabrazyme in France (total of 1200 hospital pharmacies, whereas the sample contains 300 pharmacies and was not likely to detect sales)
• Industry: of the 10 MAHs contacted, and despite their collective intention to participate, 6 provided part or all of the data requested (Actelion, Cell Therapeutics, Genzyme, Novartis, Orphan Europe, and Pfizer) for 9/12 products, 1 refused (TKT) and 2 never responded (Pierre Fabre, Shering Plough)
• Patient organisations: key contact persons do not always know where to find the information.
• Pharmacists (directly contacted by Eurodis)
• Hospital pharmacies that deliver all 12 OMPs considered are extremely rare.
• A survey among them should involve large numbers of pharmacists
• National Competent Authorities: they can inform on the achievement of negotiation phase on price and reimbursement, but have very little information on actual availability or use of the products.

The possible explanations of inter-country delays are numerous

1. Firstly, the pricing mechanisms as provided for in national regulation schemes differ from one country to the other. In some countries it is the average price from the prices already negotiated in other states (reference countries). In this case, as long as negotiations are still going on in the reference countries, no average can be calculated.

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference Countries</th>
<th>Basis of calculation</th>
<th>Prices re-calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td>Lowest price in Europe</td>
<td>Lowest price in Europe</td>
<td>No</td>
</tr>
<tr>
<td>Ireland</td>
<td>Denmark, France, Germany, Netherlands, UK</td>
<td>Lowest of average and UK price</td>
<td>No</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Belgium, France, Germany, UK</td>
<td>average</td>
<td>Yes</td>
</tr>
<tr>
<td>Portugal</td>
<td>France, Italy, Spain</td>
<td>Lowest</td>
<td>No</td>
</tr>
</tbody>
</table>

Panos Kanavos, LSE Health and Social Care 2001

Drugs are not all distributed through the same channel: complex named patient basis system, case by case reimbursement scheme, special fund for severe diseases, private or public purchasers etc. For each system, and several different systems can coexist in a same region, the decision is a complex process, often not transparent.

2. Secondly, rare diseases are not yet a public health priority in most of the 25 member states and 3 EEE countries, although regulation calls for specific national policies incentives.

3. Thirdly, not the price itself, but the accountability of pharmacies is source of extra-delays:

• Whether large or small sales volumes, hospital pharmacies have to budget the purchasing
When the decision of purchasing products depends on an annual budget, the head of the pharmacy has to select the patients he/she can afford to purchase drugs for:

- For an OMP that costs 150,000 € per patient per year, 600,000 € are needed to treat 4 patients
- With the same amount, 50 people with HIV infection can be treated each year.

**PROPOSALS TO EASE THE PROCESS**

- Establishing a new EU Committee or a subgroup of the EU Transparency Committee:
- To complete assessment of the Therapeutic Added Value (TAV) of each orphan drug
- To propose a reasonable European catalogue price based on discussion with the marketing authorisation holder

**THE NEXT STEP: TO BETTER DOCUMENT ON THE AVAILABILITY OF AUTHORISED PRODUCTS**

Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use, and establishing a European Medicines Agency, confers to EMEA a role in documenting on real use of marketed products:

- Article 13: Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Community level, broken down by Member States, and any data in the holder’s possession relating to the volume of prescriptions.

**CONCLUSIONS**

The failure of most of member states to place on the market in due legal time most of orphan products approved through the centralised procedure is striking.

From our survey, it appeared that no single source or easily accessible sources are able to provide the information needed on drug availability. The channel to place orphan drugs on the market is complex, even Marketing Authorisations holders have difficulties in obtaining information on their own products (definition of availability, co-marketing, distributors, imports…)

A structured data collection system is needed and there is a possible collaboration with EuroMedStat on this matter. Lastly, access to existing and authorised medicines is the patient first priority. National pricing and reimbursement negotiations are too often reducing the pace for accessing them.

**Views of a health care system:**

**The NICE approach to rare diseases**

**WHAT IS NICE?**

The National Institute for Health and Clinical Excellence (NICE) is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

It was created 1st April 1999 to set national clinical standards and manage new interventions appropriately into the National Health Care System NHS. New expensive interventions were not coming in as equitably, fairly and rapidly as they should have.

It has three centres:

- Centre for Public Health Excellence: elaborates guidelines on public health interventions, for actions on individuals and populations
- Centre for Health Technology Evaluation: evaluates the cost effectiveness of drugs, their safety, technology appraisals, interventional procedures
- Centre for Clinical Practice: clinical guidelines on patient management

**THE NICE APPROACH**

- Evidence based (safety, effectiveness and cost effectiveness in particular). NICE is not evaluating the costs, as affordability is a governmental responsibility. NICE is assessing the relative benefits of an intervention over its adverse reactions, and the overall value to health services.
- Transparent (scientific and social values): as these decisions are important, all groups have the right to participate in the decision process.
- Inclusive (all stakeholders)

**BACKGROUND TO NICE ASSESSING INTERVENTIONS IN RARE DISEASES**

“The Department of Health and the Welsh Assembly Government have asked NICE what approach it would take if asked to appraise orphan drugs”.

---

**SPK 110**

*Prof. Peter Littlejohns, Clinical and Public Health Director, the National Institute for Clinical Excellence, UK.*
During the last six years, NICE assessed the value of marketed orphan products as shown in figure 27 below. Some of them were considered as non cost effective and were not supported by the centre (bars in red), others, though expensive, but highly cost effective, were supported (bars in green). Data shown represent the cost in £ per quality-adjusted life-year QALY or life years gained LYG.

Are there interventions that are both very rare and very expensive? For the Ultra-orphan drugs, NICE took the decision to assess interventions responding to a more strict definition: “Products for conditions with a prevalence of less than 1 in 50,000”, or put another way, “Products for conditions with less than 1000 cases in the UK”. This was the case for the following orphan drugs:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>UK prevalent cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>Dietary modification</td>
<td>500</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>Nonacog alfa</td>
<td>380</td>
</tr>
<tr>
<td>Gaucher’s disease (type 1)</td>
<td>Imiglucerase Miglustat</td>
<td>200</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>Fabrazyme Miglustat</td>
<td>70-140</td>
</tr>
<tr>
<td>Mucopolysaccharidos (type 1)</td>
<td>Laronidase</td>
<td>500</td>
</tr>
</tbody>
</table>

Cost effectiveness appraisal consists in balancing the value of the product with quality of life. There is no automatic threshold, no cost above which a drug is declared non cost effective. There is a probability as the cost gets more and more that takes into account other factors than cost effectiveness: equity, fairness, which the drug has or not, if this is the only drug for the condition... These are not economical values, there are not produced by calculation. Instead, the process consists in a large and open discussion where all parties can express their views.

The consultation with citizens drew some useful conclusions: There is a public expectation that the NHS should be prepared to meet the reasonable treatment costs of expensive treatments for ultra-orphan conditions. Two caveats were listed:

- Commercial prices charged by manufacturers are reasonable.
- Opportunity costs are tolerable.

A feasibility study was conducted with the industry to check whether these principles were realistic. The phases of the feasibility study were:

- To assess the evidence on clinical and cost effectiveness of the use of Enzyme Replacement Therapy for the treatment of type 1 Gaucher’s disease
- To organise an Appraisal Meeting which was separate from and additional to normal programme
The Italian Medicines Agency strategy for research and rare diseases is based on several specific actions:

- A specific fund is dedicated to rare diseases (subparagraph 19 of article 48 of the law establishing the Italian Medicines Agency).
- A percentage of this fund must be devoted to research on the use of drugs.
- 50% will be used to set up a national fund for orphan drugs and drugs not yet authorised and representing the hope of a treatment for severe diseases.
- The remaining 50% will be used for:
  - implementing a National Centre of independent information on drugs
  - implementing a program of active pharmacovigilance aiming at advising and educating general practitioners and paediatricians
  - implementing research on the use of drugs and in particular head to head comparisons between drugs for the demonstration of the added therapeutic value, including for orphan drugs

Currently, 9 EU marketed orphan drugs are 100% reimbursed in Italy (Somavert (Pegvisomant), Zavesca (Miglustat), Aldurazyme (Laronidase), Carbaglu (carbaglumic acid), Ventavis (iloprost), Fabrazyme (_-galactosidase A), Trisenox (Arsenic Trioxide), Tracleer (Bosentan), and Glivec (Imatinib)).

National incentives for the research and development of orphan products: Spain

Measures for availability of orphan drugs and research, information and support for rare disease.

The author exposed the measures taken in Spain that directly or indirectly favour research, availability and information of drugs aimed for treatment, prevention and diagnosis of rare diseases. The Spanish national laws had paid attention to the needs of “certain group of patients” but since the publication of Regulation EC 141/2000 the attention is paid specifically for rare diseases, with an increasing number of different measures.

In the field of rare diseases, national laws give the general rules and the Autonomous Communities have the power to develop these laws, but there is a diversity of measures according to different policies on rare diseases. Some Communities have enlarged the rights of patients. The difficulties to access this information, due to the regionalisation of health policy, and to the fact that some measures are not published, are major.
### AVAILABILITY OF TREATMENTS AND OTHER SOCIAL MEASURES

<table>
<thead>
<tr>
<th>National Rules</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Decree 1348/2003 of 31/10/2003, BOE 04/11/2003</td>
<td>It adapts the classification of drugs to the ATC. It includes many drugs in the list of non reimbursable, but there can be exceptions in the case of orphan drugs. The law 25/1990 on medicinal products (art 94) and the Royal Decree 83/1993 on medicinal products reimbursement had previously contemplated the case for “certain groups of patients”.</td>
</tr>
<tr>
<td>Ministerial Order of 30/04/1997, BOE of 14/06/1997</td>
<td>It regulates dietitian care and nutrition. It includes metabolic diseases in the list of diseases that can be reimbursed.</td>
</tr>
<tr>
<td>Ministerial Order of 03/03/1999</td>
<td>It regulates oxygen therapy at home. It includes treatment using aerosol for cystic fibrosis.</td>
</tr>
<tr>
<td>Resolution 17/09/2004, BOE 10/11/2004</td>
<td>Financial support for different NGO. It includes support for the activities of Federacion Española de Enfermedades Raras (Rare Diseases Spanish Federation). Support renewed every year.</td>
</tr>
</tbody>
</table>

**Regional rules**

- **Galicia**: Law 7/2003 of 09/12/2003, BOE 19/12/2003 - Healthcare Law. It establishes that rare diseases patients have the right to specific healthcare programs, carried out through public healthcare centres.
- **Balearic Islands**: Order 11/04/2002, BOIB 23/04/2002 - It establishes support for the implementation of projects managed by the Instituto Balear de Asuntos Sociales. The regional government gives priority to rare diseases when deciding which projects are financed.
- **Catalonia**: Order 10/12/2002, BOG 19/12/2002 - Cystic fibrosis: It regulates oxygen therapy at home. It includes cystic fibrosis as a Social Security service
- **Valencia**: Resolution 31/07/2001, DOGV 14/08/2001 - Cystic fibrosis: It regulates the creation of special units for pharmaceutical products. Cystic fibrosis considered as a priority.
- **Galicia**: Decree 1235/2005 of 03/02/2005, DOGal 07/02/2005 - Alpha-1 Antitrypsin deficiency: Creation of an advisory committee. Responsible for criteria about pharmaceutical treatment.
- **Extremadura**: Resolution of 17/02/2003, DOE of 08/03/2003 - Multiple Sclerosis: social projects for persons with disability. It establishes a support project for patients.
- **Extremadura**: Resolution 21/02/2005, DOE 08/03/2005 - Autism: agreement on social volunteers training. Support for a specific project.

### 7 ACCESSING APPROPRIATE CARE: organisation of care

#### 7.1 Disability: are financial compensations adapted to Rare Diseases?

Rare diseases patient needs are not well taken into consideration and too often poorly reimbursed. According to Rosa Sanchez de Vega, financial compensations are not adapted to rare diseases, as medical knowledge is too limited for most of them. Rare disease patients have special needs that should be covered by the Public Health System.

In most EU countries, financial compensations are granted on the basis of the evaluation of the disability degree. If the disability degree is not well evaluated, because the doctor in charge of this evaluation does not know the disease in depth: origin, prognosis, treatment, caused impairment, acute/chronic phases, the patient will not receive sufficient financial compensations or the invalidity benefit.

She listed some of the different types of care that patients with rare diseases may need at any given time during the course of their disease. This list immediately raises the issue of the coverage by health care and social systems in the EU.