

**Biotechnology and Quality of Life:  
Orphan Medicinal Products –  
a Challenge for Health Care Systems in  
CEE Countries**

Working Round Table at the 6<sup>th</sup> International Biotech Conference  
Cavtat, Croatia  
11<sup>th</sup> October 2003

*Health care systems in countries in development, like in Central and Eastern Europe face challenges to find the optimal solution to treat patients suffering from rare disorders.*

*The aim of this working roundtable is to discuss these challenges in providing the treatment for patients suffering from rare disorders, but also to debate about the perspectives for health care systems in CEE countries to overcome these challenges.*



**A Round Table held in Cavtat, Croatia, in October 2003, addressed the challenges that Central and Eastern European (CEE) countries have in reimbursing orphan medicinal products. Physicians from CEE countries and representatives of industry and patient organisations presented their experience with rare diseases and their ideas with respect to treatment.**

Every disease whose prevalence is less than 5 patients for 10 000 persons is called a rare or orphan disorder. Today, we are counting more than 6000 rare disorders, most of them ranging from severe to very severe. They can have various forms: chronic, progressive, disabling, often life-threatening, especially in children. They can occur at any time in life. For most of them, there is no treatment and 80% of them are of genetic origin. They affect some 4% of the European population. Due to progress in genetics and biotechnology, treatments are now available for several of these rare diseases. However, the costs of treatment are very high due to the low number of patients. As explained by Dr. Ute Stölzle of Genzyme Central and Eastern Europe, the development of a new medicine takes 7 – 12 years with average costs of around 800 million Euros. Since there is only a small group of patients there is little prospect for fair return on the investments in research and development. Only with the existing orphan drug regulations and the high prices for the drugs, companies can earn enough money to invest in the development of new orphan drugs. To build a valid health care system for orphan drugs, industry should be working with physicians, the Ministry of Health, and patient organisations.

Ines Kvaternik Jenko informed the audience about Gaucher disease and patients in Slovenia, while Prof. Anna Tylki-Szymanska from Poland spoke about the patients they treat with MPS I disease. In both countries it was very difficult to obtain reimbursement for the treatment of these diseases. Only by organising very active patient organisations was it possible.

A way to reimburse the high costs of rare disease was realised in Croatia by setting up a fund for expensive drugs in which both the Ministry of Health and the insurance companies are participating. Dr. Mirando Mrsić from the University Hospital in Zagreb, Croatia, explained that with this fund patients have an equal chance to be treated and also are treated in the same standard way. He further stressed that rare diseases are not habit related or the consequence of an occupational hazard or the environment. They are just genetics and should therefore be treated. Also Prof. Ana Stavljenic-Rukavina from Zagreb, Croatia stressed that nobody could be denied the benefits of medical progress simply because the affliction from which they suffer affects only a small number of people. The public authorities should provide the necessary incentives and adapt their administrative procedures to make it possible to provide these patients with medicinal products and the highest degree of quality of life. The best strategy to achieve this is to increase overall knowledge of rare disorders, their epidemiology, pathology, prevention and treatment. This can be obtained with a freely accessible database like the Orphanet about which Dr. Ségolène Aymé from INSERM, Paris, France gave a presentation. This database is an encyclopaedia of medical knowledge authored and peer-reviewed by more than 400 experts, as well as a directory service of clinics, laboratories, research, clinical trials, and support groups.

The European Biotechnology Industry Association represents globally operating biotech-based companies and 1200 small companies through national associations. Dr. Erik Tambuyzer, Chair of the healthcare Board of EuropaBio explained that biotechnology has both an economic as a social impact on healthcare systems.

Innovation in biotechnology provides more targeted and more customised care, but healthcare budgets favour more standardisation, older (cheaper) therapies and short term solutions. The orphan drug regulations in both the USA and the European Union have been instrumental in the growth of the number of biotechnology companies and the availability of orphan medicines for rare diseases. This type of regulation should also be adopted in the CEE countries, leading to innovative and sustainable industries in these countries.

All speakers emphasised the importance of partnerships between patients, industry, healthcare professionals, insurance companies, and policy makers to come to a fair treatment of patients with a rare disease. This partnership is partly pioneered by EPPOSI, the European Platform for Patients' Organisations Science and Industries. The Chair and founder of EPPOSI, Ysbrand Poortman, gave his vision on how progress in genetics, molecular biology, and new medical technologies can provide new diagnosis and effective therapies. It is important to improve the participation of families and patients in funding for research as well as to improve the participation of public in decision making policy. EPPOSI organises workshops and conferences, publishes position papers and publications, and provides its vision to the European Commission and Parliament.

*An European research effort should be made to apply scientific progress to an innovative, affordable, and safe treatment for rare diseases.*

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## **Challenges and perspectives in the treatment of rare disorders in CEE countries – Ana Stavljenic-Rukavina, Prof. Dr.**

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In general, people expect that the health system and health professionals provide for their physical, mental, and social health and for their quality of life in a fair way.

Public health care is the responsibility of the member states and their governments, but is also subject of international law. The international humanitarian law and especially the international human rights law define the “human right to health”. International health organisations have played an important role in global public health, however patients and citizens in general are active policy makers in health care. In the current European social model it is defined that health coverage should be universal. Good health for everyone will promote social cohesion and equal access for everyone to the health care system should be actively pursued. Health care should be regarded as a service, and not as an industry. From this social model, an European Union health policy has emerged stating that everyone should be in a position to benefit from systems to promote health care, to treat illness, and to provide care and rehabilitation for those who need it. The treaty guarantee free movement of people (health professionals, patients), goods (technology, pharmaceuticals), and services (payers, providers).

Through the idea of globalisation the world would be created as a single entity by making social, economic, political, environmental laws across spatial, temporal and cognitive boundaries. It is unknown yet what impact globalisation processes will have on public health in the Central & Eastern European (CEE) countries where total expenditure on health are 4-10% of BNP but in absolute amount 70-600 US \$ per capita (10-20% of amount spend in EU). The health care system in some countries is in the process of reforming according to some basic principles. First of all it is centred on people and driven by the principles of human dignity, equity, solidarity and ethics. Reforms are focused on quality as measured by the receivers of care and by providers. The system should be based on sustainable financing, which provides equitable access to necessary care for all patients.

The challenges however lie in the treatment of rare disorders in CEE countries. A society, even those in transition like many of the CEE countries, should not accept that certain individuals be denied the benefits of medical progress simply because the affliction from which they suffer affects only a small number of people. It is therefore up to the public authorities to provide the necessary incentives and to adapt their administrative procedures to make it possible to provide these patients with medicinal products and meet to the highest degree of quality of life for them.

The best strategy to achieve this is to increase overall knowledge of rare disorders, their epidemiology, pathology, prevention and treatment. Professionals and non-governmental organisations (NGOs) should break down the stigma that rare and inherited disorders have in the general public and families of patients. Furthermore, diagnostic capacities should be improved using a network of laboratories on country, regional and European level.

Also the legal background for the application of medicinal products (safety and risk management) has to be improved as well as the funding. For example by reallocation of funds, working with sponsors, and an adapted tax policy. Special funds for research on rare disorders might be constituted and the criteria for more rapid and predictive clinical trials should be altered. The strategy should further improve the participation of families and patients in the funding for research and increase the participation of the public in decision making policy. Finally, all countries should contribute to database registries on the regional and the European level.

The European Union (EU) should support the CEE countries in their research of pathogenesis and clinical characterisation of rare diseases, the identification of genetic and environmental factors, the improvement of molecular and clinical diagnosis, and give support for database registries. A network system must be formed to exchange information and learn from best practice, accepting that overall harmonisation might be impossible.

A model for Europe-wide collaboration in rare disorders must be set up in which science, industry, community, and policy makers participate.

*“If not us, who? If not now, when?” (Primo Levi)*

## Living with a Rare Disorder - Ines Kvaternik Jenko

*Gaucher Patient Association Slovenia*



**Figure 1: Gaucher patient S.S. (Poland): Pre-treatment (1997)**



**Figure 2: Gaucher patient S.S. (Poland): Post-treatment (2003)**

On behalf of Ines Kvaternik, the presentation was presented by **Grzegorz Wegrzyn** from Gdansk, Poland.

Gaucher disease is a rare genetic disorder with an incidence of 1 in 50,000. Due to the absence of a lysosomal enzyme there is an accumulation of a fatty substance called glucocerebroside in the cells of the body. The cells with the accumulated substrate are called Gaucher cells. These cells will affect the growth and function of many organs and tissues. The liver and the spleen will enlarge ten-fold, the skeleton is affected causing osteonecrosis and chronic bone pain, and the blood is abnormal with anaemia and a tendency to bleed and bruise.

Since 1991 a treatment is available in the USA, imiglucerase (Cerezyme<sup>®</sup>), which replaces the missing enzyme. This so called enzyme replacement therapy (ERT) can -in a safe and effective way- halt or normalise many of the major signs and symptoms of the disease. The product has been on the market in Europe since 1993.

In Slovenia, 5 patients (all children) started for the first time with ERT, but, due to the high costs, the therapy was discontinued in 1995. With the support of physicians and patients the therapy was restarted in 1997.

At this moment, 13 patients have been diagnosed with Gaucher disease (Slovenia is a small country with 1.9 million inhabitants)

When the patients and physicians group started to bring Gaucher disease under the attention of the public, there was no social acceptance because there was no knowledge and awareness of disease and treatment. Therefore several activities were started. Patients contacted Gaucher patients from Europe and learned more about Gaucher disease and therapy. Patients also started to fight for therapy by writing letters to insurers and government.

At the beginning of February 2003, the Sick Fund of Slovenia approved the Enzyme Replacement Therapy. Recently 4 new adult patients were diagnosed (age 32 - 55 years) with severe progress of the disease, whose therapy could start directly in February 2003.

Recently, Slovenian patients are becoming more and more active. On 20 February 2003 the Gaucher disease organisation was established and Fabry patients from Slovenia are encouraged to organise themselves. Patients participated on the first meeting of Metabolic Patient Society, Croatia in Poreč on May 2003. Many more physicians in Slovenia have been involved in supplying ERT.

The following action plan was recently formulated. The Society will continue its partnership with University Hospital Zagreb, patient organisations like the European Gaucher Alliance (EGA) and the pharmaceutical industry. Since Slovenia is a small country it needs a strong patient advocacy, which can only be reached by combining forces with other national patient alliances.

The main goal of the society is that patients with a rare disease can live a normal life, have a future and perspectives. Therefore it is needed to fight for the right of patients and for optimal treatment and care for every citizen. The association will have to become a reliable partner within the EGA and continue good cooperation with physicians, scientists, industry, and patient organisations.

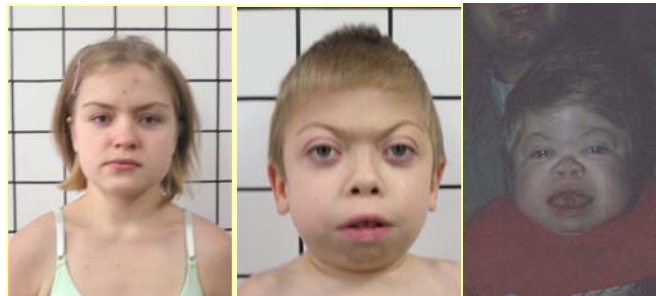
As a conclusion to this presentation, Grzegorz Wegrzyn told a parallel story about the development and activities of an MPS patient organisation in Poland. MPS I is another rare disease for which recently a drug came on the market. The daughter of Grzegorz Wegrzyn has MPS I disease and because of the fight for reimbursement by the patient and physician group, she and 3 other patients were recently started on ERT.

## Achievements and Constraints on the Quality of Life of Patients with Rare Metabolic Disorders – Anna Tylki-Szymańska, Prof. Dr.

*Department of Metabolic Diseases, The Children's Memorial Health Institute Warsaw, Poland*

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After over 20 years of experience in diagnosing, managing, and treating patients with various metabolic and genetic diseases, some suggestions can be put forward as to the directions in which diagnostic and treatment methods should go. The advances in knowledge about genetic diseases or genetically determined metabolic diseases have been snowballing over recent decades. For example, the Handbook of Metabolic and Inherited Disease has increased four times in volume in the past 20 years.



**Three children with MPS I disease ranging from mild to very severe**

With rare genetic disorders, the same genetic defect can give clinically very different pictures. The natural history, or course, of the same disease may also differ greatly. In the hospital, amazing spectrums of symptoms ranging from very mild to very serious are observed (Figure 3).

Clinical evaluation can not, however, be the only basis for suggesting a diagnosis. This is why we use so-called selective screening, which is based on screening for a characteristic biochemical marker in cases where a symptom suggests that a given disease is present.

In some countries, selective screening is beginning to evolve into population screening. This might be expensive, but in some cases, early and prompt diagnosis of metabolic diseases can significantly diminish the costs of treatment later on. Early detection of genetic diseases carrying a high risk of recurrence in the family is important not only in terms of treatment of the affected child, but it also permits early genetic consultation for the parents. They can then make informed decisions in terms of having (more) children.

The prevalence of genetic diseases is always the outcome of the true incidence in a given population and the effectiveness of diagnosis. The rising prevalence of these diseases is not only due to the expansion of knowledge in clinical terms, but also to the development of new technologies, which applied to diagnostic methods, make it possible to identify completely unknown diseases or those known to date only as syndromes. These diseases can now be diagnosed as a specific rare genetic disease. The increased frequency of diagnosis of genetically determined diseases means that many of them are becoming more than just case reports.

These rare genetic diseases form a group of diseases that are rare but frequent and serious enough to merit a special approach from the medical aspect and special systemic solutions, i.e. social and economic solutions. Knowledge about the details of these diseases is on the rise among patients themselves and their families, as well as society. One of the signs of this are the numerous grass-roots movements, such as patient organisations.

As knowledge about rare diseases increased, several new methods of treatment were developed, including treatments targeting the underlying cause of the disease.

These include enzyme replacement therapy in lysosomal diseases and other therapeutic approaches such as organ transplants, special dietary products in elimination diets, drugs inhibiting the synthesis of substrates or products of metabolic pathways. These drugs, like the diseases they treat, are called orphan drugs, and are usually extremely expensive.

Doctors view the fact that these diseases have become treatable as an enormous success both in terms of medical progress and personal satisfaction.

The feeling of helplessness when unable to propose an effective treatment is exceedingly frustrating for a doctor.

It can be said that the appearance of therapeutic possibilities in certain diseases solves not only the problem for the patient and his family, but also in a very meaningful way, the helplessness of the doctor.

In their medical practice, doctors naturally aim to use new, effective treatments. In the case of orphan diseases, the limited access to a treatment, in many cases for economic reasons is exceedingly frustrating and humiliating for a doctor.

A bond of solidarity between the doctor and the patient is natural when it comes to treatment even with very expensive drugs, and in both cases lack of access to the treatment for economic reasons undermines the self-esteem of both the patient and the doctor.

On the other hand, doctors are aware of the rising costs of medical treatment and understand the economic difficulties involved in introducing new drugs and new diagnostic methods.

They can not, however, decide not to help their patients to the best of their ability. The general public should be convinced that genetically determined metabolic diseases can be effectively treated.

This information should reach political circles, so that despite the high costs, money for treatment of genetic diseases is allocated in national budgets. This requires the development of systemic solutions to meet these challenges. This is important because aside from the therapeutic and social aspects, developing and financing procedures of this sort is an important intellectual investment. Even in affluent countries we observe a trend to lower treatment costs, but the benefits of medical progress can not be sacrificed for economy.

*„... if progress is not accompanied by political good will, it leads to inequality. Political will is therefore necessary to prevent knowledge from increasing inequality. ”*

**(Prof A. Khan** lectured delivered in Warsaw 2001)

**Diagnosis of rare diseases. How to overcome current difficulties? - Ségolène Aymé, Dr.**  
*INSERM SC11 – Orphanet, Paris – France*

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Rare diseases are an emerging concept within Europe. It was recognised at the EU level in 1999 by the adoption of a regulation on orphan drugs. A program of action was launched by the Directorate General for Public Health in France and a call for research proposals by Directorate General for Research. The reason for this activities was that these rare genetic diseases are life-threatening and therefore costly. Furthermore, these model diseases could be seen as a source of biotechnological innovation for the pharmaceutical industry. Finally, politics became involved because these diseases were given high priorities by the citizens.

Patients with rare genetic diseases complain about late and inaccurate diagnoses, because the consequences are psychological suffering, many unnecessary investigations and inadequate care. Furthermore, they are not able to make an informed choice to have or not to have children.

There are more than 3,000 rare diseases and 3-5 new ones are described every week. They are very heterogeneous with 80% of them being genetically determined. They appear mainly in infancy and childhood (2/3), are chronic and 63% of them are life-threatening diseases. Each of them is rare but all together, they represent 5% of the European population. Most diagnoses are based on clinical features, but there is hardly any teaching at medical school.

At this moment, 1,200 genes are identified, but there are only 300 clinical tests which are very costly.

Only a few European networks and data collections exist because of too few clinical experts, which are difficult to identify. The health care services are unorganised with respect to rare diseases. This organisation should also not be done on a regional basis but on an European level is necessary.

To improve the current situation, clinical research should be boosted and the collaboration between and forming of networks should be encouraged. Furthermore, repositories of clinical and biological data as open resources for research should be established.

A first step to communicate and provide reliable and up to date information to all stakeholders with easy access is the European database of rare diseases called Orphanet ([www.orpha.net](http://www.orpha.net)). Orphanet is funded by the European commission, the Ministry of Health of France, and INSERM. The editorial board is formed by 120 experts from all European countries who cover all specialties.

This database is on the one hand an encyclopaedia of medical knowledge authored and peer-reviewed by more than 500 experts, on the other hand it contains a directory service of clinics, laboratories, research, clinical trials, and support groups.

The website is accessed daily by 5000 users, who are patients or their family (45%), rare healthcare professionals (40%), other types of professionals (6%) and people close to a patient but not related (8%). Expert clinicians and biologists are using the website to identify a diagnostic lab, to refer a patient to an other clinician, to give information on support groups to patients, to learn more about a rare disease, and/or to identify a researcher.

Orphanet has set up partnerships with the patient organisations Eurordis and National Alliances, who are involved in data collection and the validation process. When patients need to be transported for clinical purpose and if medically justified, free tickets from Air France can be obtained. Together with insurance companies education tools are developed and with pharmaceutical and biotech industry R&D opportunities are identified.

To set up collaboration with the CEE countries, partners are to be identified in each country.

These partners will get the task to identify committed experts from the country to act as scientific advisors, to obtain support from health authorities, and to collect data. These partners will get support from the central registry by supplying procedures and informatics tools. Further they will be trained and invited to partner meetings.

Gathering information requires expertise and long-term efforts which is only possible at the European level. This information is a key issue in the field of rare diseases:

- To improve diagnosis and treatment
- To speed up research
- To contribute to empowering consumers
- To improve right use of clinical resources

## **Perspectives of the contribution of biotechnology to healthcare in Central and Eastern Europe - Erik Tambuyzer, PhD**

*Chair Health Care Board, EuropaBio*

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EuropaBio is the European Biotechnology Industry Association ([www.europabio.org](http://www.europabio.org)) representing 35 globally operating biotech-based companies and 23 national associations, totalling 1200 small and medium sized enterprises (including in CEE countries). The members are involved in all biotechnology applications including those for human health care. EuropaBio's mission is to increase the competitiveness of the innovative and responsible biotechnology-based industry in Europe. It is committed to an open, informed dialogue with all stakeholders about the ethical, social and economic aspects of biotechnology and its applications.

EuropaBio is active in some of the CEE countries. Contacts have been made with the Hungarian Biotech Association (HBA), with the Slovenian Council for Life Sciences and a representative of the Slovenian government, with Czech Invest in Prague Czech Republic and also with Estland.

EuropaBio is very interested to have further contacts with representatives of other CEE countries, like Croatia. Therefore contact can be made with the EuropaBio Secretary-General ([j.vanhemelrijck@europabio.org](mailto:j.vanhemelrijck@europabio.org)).

Currently, applications of biotechnology in healthcare are numerous:

- Diagnostic kits, prognostics, theranostics.
- Genetic testing for single genes and for predispositional testing;
- pharmacogenetics & pharmacogenomics.
- Biopharmaceuticals for common and for rare diseases; combination products of devices with tissues or biological medicines.
- Recombinant vaccines.
- DNA and RNA in gene therapy or other applications.
- Cell and tissue-based products (based on viable autologous or allogenic cells, stem cells).
- Biosurgery, biomaterials.
- Bioinformatics, nanobiotechnology.
- Process and manufacturing tools.

Healthcare systems as well as regulatory authorities and legislation are adapting to boundary-crossing products such as:

- Medical devices and medicinal products: e.g. cell and tissue-based products, biodegrading devices;
- Surgical techniques and medicinal products: e.g. biosurgery;
- Services and products: e.g. autologous cell therapies, cancer vaccines;
- Diagnostics and therapeutics: e.g. therapeutics monitoring.

For many of these products it is not clear to which class they belong, for example it is still being discussed if autologous cartilage replacement in joints is a medicine, a medical device, or a service (medical procedure).

There is an increasing discussion about how costly the development of a medicine is, and about speed of marketing authorisation versus potential risk, especially for life-threatening or seriously debilitating diseases. Furthermore, the issue of compassionate use of a life-saving not yet registered treatment is a pressing topic. There is a rising need for consistency of registration requirements across countries with respect to these issues.

Worldwide there are several important health care issues.

- The safety, quality and efficacy of biological medicines and non-medicine health care products should be guaranteed by regulations to ensure public confidence in healthcare products and their approval.
- For all providers of medicinal products, i.e. industry, academia, hospitals and tissue banks, the same rules and benefits should apply.
- Impartial and timely access for patients to treatments of serious diseases are becoming ethical issues. Safety of a drug is a different issue for patients with a life-threatening disease.
- The higher prices of innovative medicines may be offset by higher efficacy and less side effects plus less social costs, keeping people active and healthy.

In 1983 the Orphan Drug Act was implemented in the USA, which has resulted so far in over 270 approved products, helping over 12 million patients. Many biotech companies rely on orphan drug market exclusivity. In fact, a large number of biotechnology firms have been established as a result of the U.S. Orphan Drug Act as was mentioned by Dr. M. Haffner, Director of the FDA Office of Orphan Products Development.

Of all biopharmaceuticals approved in the US by FDA between 1995-2000, 46 % were orphan medicines. This trend is also happening in Europe as a result of the orphan medicinal products regulation (COMP), which was passed in December 1999.

*“One additional orphan drug approval is estimated to have prevented 211 deaths in the subsequent year.”* (NBER Working Paper No. 8677).

What people in Europe know and how people think about orphan products and rare diseases can be learnt from a Takeda/OrphaNet survey held in France. More than 1000 French citizens over 15 years of age were questioned. It turned out that 25 % of the population is directly or indirectly in contact with persons affected by rare diseases. The persons questioned considered research into rare diseases as more important than some other issues such as improving meat quality, or research on genetically modified organisms, and as equally important as efforts to improve road safety or to limit smoking tobacco. Of the interviewed people, 85 % was ready to contribute to and support this type of research. They believe that rare disease research should be funded by both government and industry.

Biotechnology has both an economic and a social impact on healthcare systems.

While biotechnology innovation provides more targeted and more customised care, healthcare budgets progress the opposite way, towards standardisation, favouring de facto old(er) therapies and short term solutions. Health care cost-effectiveness may have a different time horizon than the interests of patients, or the economic interests of society at large.

The cost for innovative medicines may be offset by higher efficacy and less side effects providing less social costs, keeping people active and healthy.

Good health of the population is proven to be an economic driver: measures to improve health will therefore benefit the economy.

Patients, even those with rare diseases, organize themselves in associations and umbrella organisations and demand a voice in the health care debates, and start to impact this debate.

Through the orphan medicinal products regulation European patient representatives for the first time take part in Commission policy and EMEA regulatory discussions for innovative medicines. Patients, scientists and industry engage in consensus building and collaborate to ensure a dialogue about new technologies e.g. through initiatives like EPPOSI, the European Platform for Patients' Organisations, Science and Industry.

Perspectives for CEE countries

Of high importance is to use the existing research and clinical base and strengths of CEE countries to participate in the development of innovation. Concentrating mainly on copy products (generics), will not pay off over the long term.

Because of the low prevalence, but also because of the severity of rare diseases, orphan medicines may be good pilot projects for CEE countries to adapt their healthcare systems while integrating in the EU. These products allow innovative, out of the box approaches, in terms of regulations, patient access and partnerships with different stakeholders. And most orphan medicines are for very serious and life-threatening diseases and offer a treatment for these diseases with a remarkable impact on the patients, for the first time in human history. These approaches are also increasingly showing the way forward for approaches to innovative medicines in general.

Patient representatives from CEE countries should be encouraged to work with their counterparts of Western European countries and discuss involvement in health system debates.

Fostering entrepreneurship in industry, academia and even patient groups makes a difference for society everywhere in the world.

**Industry perspective on bringing orphan medicines to the patients - Ute Stölzle, Dr.***Vice President-General Manager Genzyme Central and Eastern Europe*

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Orphan medicines are products for the treatment of rare diseases (also called orphan diseases). These diseases are serious, life-threatening or chronically debilitating diseases with a prevalence of less than 5 per 10.000 in the European Community.

Everyone will agree that patients with rare diseases have the same right to quality treatments as patients with common diseases like heart failure or diabetes.

Genzyme is a biotechnology company with the philosophy to provide solutions for unmet medical needs. During the last 20 years several medicines for rare diseases have been developed. Normally this development takes 7 – 12 years and costs around 800 million Euros. Since there is only a small group of patients, there is little prospect for fair return on R & D investments. However, with the incentives by orphan drug regulations, companies have been encouraged to invest in the development of new orphan medicines.

Currently, Genzyme has 3 orphan drugs on the market in the USA and Europe:

Cerezyme® for Gaucher disease, Fabrazyme® for Fabry disease, and Aldurazyme® for MPS I disease. For Pompe disease, the drug Myozyme™ and for Niemann Pick B disease, not yet named, are in development. For these so called lysosomal storage diseases also substrate inhibition drugs and gene therapies are under research.

Genzyme's goal is to be partners in healthcare with physicians, healthcare providers, insurance companies (payers), and patients' organisations.

Only together the challenges of orphan drugs can be tackled. These challenges are the often late diagnosis, the missing experts, and the low number of evaluation and treatment centres. Also the resistance of the medical insurance companies to reimburse the expensive orphan drugs should be worked on by providing information. These therapies can only exist because they are expensive. Without a return on investment, pharmaceutical and biotech companies would not start development of these drugs. The reality is that the same development costs are needed for drugs that are only needed by a small patient population, as for medicines for common diseases.

Only by working with physicians, the Ministry of Health, and patient organisations, we can build a sustainable healthcare system including for the provision of orphan drugs. There should be a sense of urgency to build such a system. Many of the rare diseases are progressive and the patients should be treated before irreversible complications occur. When the therapy is available and approved it is not acceptable to wait 6 months for reimbursement to be arranged.

**Example Fabry Disease**

- Rare X linked disease; females are carriers but suffer the same life threatening complications as affected males.
- Limited awareness under physicians and public
- Average age of first symptoms (acroparesthesia): 10 years
- Average age of diagnosis: 29 years
- Number of doctors seen before final diagnosis: 9
- Onset of strokes and renal insufficiency in their 20's

These patients should have the privilege to obtain life-saving treatment.

Our mission is to take care of the patient!

**The patients role in European health policy making: Patients in partnership with science and industry - Ysbrand Poortman**

*Chairman and founder of the European Platform for Patient Organisations Science and Industries (EPPOSI)*

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In medicine there are many unmet needs and this more specifically in the field of rare disorders. The road from basic science to safe and effective treatment is long, uncertain and costly. Progress in genetics, molecular biology and new medical technologies have provided a range of options for accurate diagnosis and effective therapies. Timely and accurate diagnosis of genetic diseases is important for family planning, for prognosis, for appropriate medical care and treatment and for the accumulation of knowledge about the disease. This is specifically true and necessary for rare diseases.

At birth babies are tested for PKU while new molecular technologies now offer a range of additional bloodspot tests for another 70 or more diseases. New treatments reduce the burden of the disease.

New preventive policies opens avenues leading from disease management to health maintenance. This is f.i. possible by neonatal testing and pre symptomatic treatment. However, the access to innovative treatments for rare diseases is limited, not consistent, and very different in the various countries within Europe. It is not acceptable that patients have to wait for a long time before being treated with an effective drug, or not at all treated, while irreversible damage takes place.

It is important that patients become fully aware of their own physical condition and addition of the roadblocks and opportunities for getting treatment. That's why patients and their families need understanding and education regarding genetics and biotechnology, regarding research and development and how to influence R&D as well as how to influence healthcare systems. Patients will then no longer be passive recipients of this health care. In fact, patients have organised themselves on a national, continental, and global level in their specific fields of interest in order to play a role in the political arena. The physical, psychosocial and financial problems that patients and their families daily meet, make them experts by experience. Their large numbers, their good contacts with academia and national, continental and global representation on the one hand and their interactions with the media, the politicians, the policymakers and legislators on the other hand, give them influence.

In Europe the patient organisations have taken the initiative for a structural collaboration with science and industry. As an umbrella organisation, the European Platform for Patients Organisations, Science, and Industry (EPPOSI) unites people from these disciplines to work towards treatment and prevention of serious diseases. EPPOSI brings all parties together on hot topics, organises workshops and conferences on urgent issues, publishes reports, communicates with the European Committee and Parliament. On its website ([www.epposi.org](http://www.epposi.org)) this can all be read.

Patients' influence on EU policy decisions and outcomes and their part in the regulatory and policy process is increasing fast and many examples can be given of their effective input including in the clinical environment.

EPPOSI is a strong supporter of a major European research effort and the fast translation of scientific progress into innovative, affordable, timely and safe treatment for all serious diseases and in particular for rare disorders.

## Are rare diseases a priority for Central and Eastern Public Health? Croatian Experience - Mirando Mrsić, M. D., PhD

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Around 1-2% of all newborns have some form of inherited metabolic disorder. When the prevalence of the individual disease is less than 5 in 10.000 it is defined as a rare disease. Most of these diseases have a progressive and fatal outcome when the diagnosis is not established in time. There is further a very high risk of recurrence in families. However, there is effective treatment for some of these diseases.

Rare diseases have no ethnic predilection and are not caused by an individual habit (like smoking). They are also not the consequence of an occupational hazard or the environment.

Rare diseases are only a matter of genetics, but it will cost about 150.000 Euro per year per patient for therapy. It is estimated that the cost for the treatment of five Gaucher patients in Croatia is around 700.000 Euro per year. In the same time cost of the treatment of high blood pressure in Croatian population is up to 80.000.000 Euro. According to published statistical data we expect approximately 20-25 Gaucher patients in Croatia - the treatment costs for all 25 Gaucher patients would result in only 0.6% of the whole Croatian drug budget. On the other hand side, Gaucher patients who are not receiving the therapy will experience prolonged and often hospitalization, disability, low quality of life and will be unable to work.

In 2002 the total costs of orphan drugs took 0.35% of the Croatian drug budget, while for typical habit related diseases, statins and anti-hypertensive drugs are reimbursed costing respectively 9% and 18% of this budget (Figure 4).

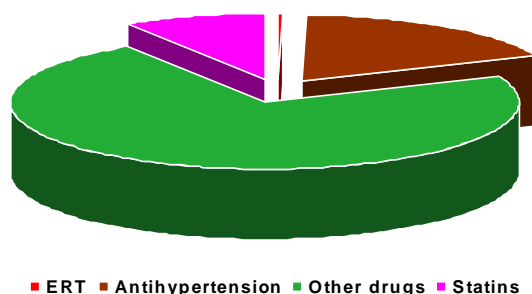
According to the constitutional law, every citizen of Croatia should have equal rights to obtain appropriate health care. With respect to rare diseases this means that the health care system should use new diagnostic tools and new therapeutic methods. Further that a new group of diseases should be defined in their rules with somewhat higher costs. The population will profit because much will be learned of the pathogenesis of disorders and about population genetics. New screening methods will become available to quickly detect rare diseases.

The individual patient will profit with a good quality of life if diagnosis is established properly and with a specific treatment (ERT; gene therapy) for some of diseases.

Health economics should be applied to calculate what the hospital costs will be for an untreated patient compared to a treated patient.

### Lysosomal storage disease (LSD)

LSD is an accumulation of substrate within the lysosome usually due to deficiency of a catabolic enzyme. There are more than 30 different LSDs of which Gaucher disease, MPS (I-VI) disease, and Fabry disease are the most frequently occurring. In the Zagreb hospital 6 patients are reported with Gaucher disease, while in Austria this is 25, in Slovenia 13, in Poland 50, and in Serbia 25.



**Figure 4: Costs of certain medicines as part of the Croatian drugs budget**

The diagnosis of a LSD is made both by clinical evaluation by neurologists, ophthalmologists, haematologists, urologists, and radiologists as well as by determination in a metabolic laboratory of enzyme products, enzymes, and genes.

A way to reimburse the high costs of rare disease was realised in Croatia by setting up a fund for expensive drugs in which both the Ministry of Health and the insurance companies participate.

An independent drug committee defines, based on rigid criteria regarding the disease prevalence in Croatia, how the money is divided over the hospitals. In the hospitals a local committee is responsible for the application.

The main goal of the fund is to offer same and equal treatment to every citizen of Croatia suffering of rare disease or a disease that require expensive and/or prolonged treatment.

With this fund, all patients have a equal chance to be treated and all patients will also have an equal treatment. Furthermore, resources and treatment can be controlled easily. A problem however with the fund is that an application for money can take 6 months.

In the budget of the hospital in Zagreb, 9% is allocated to expensive drugs for the following diseases:

- Haemophilia and other congenital bleeding disorders
- AIDS
- Adenosin-deminase deficiency
- Inherited metabolic disorders
- Multiple sclerosis
- Chronic myeloid leukaemia
- Juvenile arthritis
- Ovarian cancer
- Breast cancer
- Prostate cancer
- NHL
- Colon carcinoma
- Growth hormones