

Inventory of Community and national incentive measures to aid the research, marketing, development and availability of orphan medicinal products

Background

Regulation (EC) No. 141/2000 of the European Parliament and of the Council on Orphan medicinal products was adopted on 16th December 1999 and was published in the Official Journal of the European Communities on 22nd January 2000.¹ It entered into force on 27th April 2000, the date of adoption by the Commission of the implementing regulation foreseen in Articles 3.2 and 8.4.² Article 9 of the same regulation requires Member States to communicate to the Commission detailed information concerning any measure that have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. In addition, the Commission is required to publish a detailed inventory of all incentives made available by the Community and the Member States to support research into and availability of orphan medicinal products.

This first publication of an inventory is designed to meet the obligations of the regulation and to represent the status of such incentives immediately following the entry into force of the regulation. The information in this inventory is intended to be updated on a regular basis.

Aim of the Orphan regulation

The aim of the European Parliament and Council Regulation on Orphan Medicinal Products is to establish a Community procedure for designating orphan medicinal products and to introduce incentives for orphan medicinal products research, development and marketing, in particular by granting exclusive marketing rights for a ten year period.

In recent decades, medicine and medical research have made remarkable progress in saving lives, extending life expectancy and ridding the world of a number of diseases. The most spectacular successes of all have been in the use of vaccines to prevent childhood illnesses, in the use of antibiotics to combat infectious diseases and in the development of anti-viral medicinal products for the prevention or treatment of AIDS. Great strides have also been made in the diagnosis, prevention or treatment of cancer and cardiovascular diseases.

Nevertheless, there are still a great many diseases which cannot be treated satisfactorily and for which no medication or other diagnosis, prevention or treatment is available. In addition to the widespread and well-known diseases of this kind, there is also a whole series of diseases which affect relatively few people; approximately 5 000 such diseases have been identified. The pharmaceutical industry is reluctant to develop medicinal

¹ OJ L 18, 22.1.2000

² OJ L 103, 28.4.2000

products to treat these diseases: pharmaceutical research and development are so expensive nowadays that there is practically no chance of any company making the effort to develop a medicinal product, to obtain authorisation for its use and to place it on the market if it is to be supplied at normal prices to the few patients who require it. That is why such medicinal products are known as “orphan medicinal products”.

Society cannot 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 so as to make it as easy as possible to provide these patients with medicinal products which are just as safe and effective as any other medicinal product and meet the same quality standards.

In the United States, an incentive system for the development of orphan medicinal products (the “Orphan Drug Act”) was introduced in 1983. All designated orphan products are eligible for a federal tax credit equal to 50 % of the clinical research expenditure; orphan products are exempted from the application fee for FDA approval, and the first product authorised for a specific indication gets a seven-year marketing exclusivity period. Congress also appropriates around \$ 20 million for FDA for grants for orphan products. These measures have been very successful in stimulating the research and development of Orphan Medicinal Products, so much so that a number of other countries have sought to emulate it. A similar regime was introduced in Japan in 1995, in Singapore in 1997 and in Australia in 1998.

In the European Union, in the course of the last decade, a number of Member States have adopted specific measures to increase our knowledge of rare diseases and to improve their detection, diagnosis, prevention or treatment. In some cases, the relevant legislation or administrative provisions include a reference to the concept of “orphan drug” or “uneconomic drug”. These initiatives, however, until recently have been few and far between and have certainly not led to any significant progress in research on rare diseases.

The objective of the Orphan Regulation is to advance this progress, by introducing a number of direct incentives, but also by encouraging Member States to adopt similar and/or complementary measures at a national level.

The aim of this inventory is to collect together the measures that have been introduced both at Community level and at national level and to present this information in a transparent manner. To this end Member States have been asked to communicate details of any measures introduced or in force. In addition, information from the different services of the Commission has also been requested. This inventory is based on the information received as of end December 2000.

1. Community measures

1.1. The Regulation on Orphan Medicinal Products

The principle new measure introduced by the Community is, undoubtedly, the Regulation on Orphan Medicinal Products. Since the entry into force of this regulation, 71 applications for designation as Orphan medicinal products have been received by the European Agency for the Evaluation of Medicinal Products (the Agency) and, as of end December 2000, 26 opinions on the granting of designations had been adopted by the

Committee for Orphan Medicinal Products. 13 of these had been translated into Community decisions. 3 of the 29 products discussed as of end 2000 were unable to successfully meet the criteria of the regulation and were withdrawn by the sponsors before the adoption of opinions

A summary of the information as of end 2000 is provided in the table below:

<i>Year</i>	<i>Intent to file Notified</i>	<i>Applications submitted</i>	<i>Applications withdrawn</i>	<i>Positive COMP Opinions</i>	<i>Negative COMP Opinions</i>	<i>Designations granted by Commission</i>
2000	29	71	3	26	-	13

The principle direct incentives introduced by this regulation are as follows:

The introduction of a **designation procedure** for orphan medicinal products. Designation as an orphan medicinal product may be applied for on the basis of an application to the European Medicines Evaluation Agency (the Agency). Further details are available on the following web addresses: <http://www.eudra.org/humandocs/Humans/COMP.htm> and <http://pharmacos.eudra.org/orphanmp/index.htm>.

On the basis of this designation, the possibility of **fee waivers** from the fees relating to the marketing authorisation procedure, including from fees for the provision of protocol assistance or scientific advice, marketing authorisation, inspections, renewals etc. Further information on the amounts and procedure are available on the EMEA web-site.

The key incentive in the regulation is the 10 year **market exclusivity** provision. This is also based on the designation as an orphan medicinal product. Market exclusivity is unanimously regarded as crucial to any system of incentives for research and development work on orphan medicinal products. In the regulation, market exclusivity is granted only where the medicinal product has been designated as an orphan medicinal product by the Community and where either the Community or all 15 Member States have issued marketing authorisations in respect of the medicinal product concerned. The protection thus granted prevents the Community or a Member State from subsequently issuing a marketing authorisation for a similar medicinal product (e.g. the same active substance) and for the same indication. It does not prevent the marketing of another product for the same indication, which would constitute an unjustified restriction on therapeutic innovation, on the rights of third parties and on patient expectations.

Protocol assistance refers to the provision of scientific advice to potential applicants for marketing authorisations on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the product. The development of an orphan medicinal product may present specific problems which must be taken into account. To take but one example, it may be difficult to find enough patients willing to take part in clinical trials for a medicinal product which might be of benefit only to a very few people. Therefore the facility to have scientific advice from experienced experts prior to making an application is an important incentive designed to aid the development of an orphan medicinal product.

The regulation also provides for the possibility of a **community marketing authorisation** for a designated orphan medicinal product. This community marketing authorisation (issued by the Community under what is known as the “centralised procedure”) is the simplest and quickest way of placing medicinal product on the market throughout the Community. The regulation gives Orphan medicinal products (easier) access to this procedure by exempting the sponsor from the requirement to show that the medicinal product meets the conditions set out in the Annex to Regulation (EEC) No 2309/93.

The regulation sets up a **Committee for Orphan Medicinal Products (COMP)**. It is this committee which is responsible for the scientific examination leading to designation of an Orphan Medicinal Product. The COMP has been in operation since April 2000. In the course of its designation work, the COMP has identified **experts on specific orphan diseases** and a database of these experts is being established. The aim of this exercise is to increase the European knowledge base about rare diseases, with the intention of being able to refer to these experts during subsequent evaluation of specific products or when providing scientific advice or protocol assistance. As of end December 2000, 66 experts had been appointed by the COMP.

The orphan medicinal products designated so far include possible treatments for diseases such as Fabry disease, acute myeloid leukaemia, Gaucher disease. The full listing can be found at the following web-address: <http://pharmacos.eudra.org/register/orphreg.htm> .

1.2 Specific Community research opportunities

The Commission’s Research Directorate General is also active in its support for research into orphan medicinal products. The principal support is implemented through the Quality of Life and Management of Living Resources Programme of the 5th Framework programme. This support is provided in the form of research grants awarded on a competitive basis and selected by the Commission following an evaluation of independent experts.

In the Quality of Life programme to date, 17 projects are being supported with an overall budget of 23.5 m €. These activities are taking place in two areas: the generic activity 7 (chronic, degenerative and rare diseases research, 13 projects, 15.2 m €) and the key action 3 (cell factory, 4 projects 8.3 m €).

It should be noted that the 13 projects funded in the area of chronic, degenerative and rare diseases represent a significant 21% of projects funded under this action line, which is aimed at understanding causal mechanisms and at supporting clinical trials for most of the existing major disorders. This emphasis is the result of the notion that support for research into rare diseases is especially needed at Community level. For example, because of the low incidence of rare diseases, case numbers in individual Member States are often too low to conduct clinical trials in a meaningful time frame.

Taking into account all the 17 projects of the Quality of Life programme to date, they concern a variety of topics:

Topic	Number of Projects
Pathogenesis and clinical characterisation	most assess this issue

Identification of genetic and environmental factors	7
Development of molecular and clinical markers for diagnosis and evaluation of diagnostic tests	6
Support for clinical trials and establishment of databases and registries for rare diseases	5
Therapy of rare diseases	8

The first three topics aim at understanding the basis of rare diseases which could lead to the identification of targets suitable for the development of orphan medicinal products. The latter two directly contribute to fulfilling the regulatory requirements for the approval of orphan medicinal products.

Diseases addressed by the supported projects include myopathies, infantile hyperinsulism, defects of glycosylation, Parkinson's plus syndromes, Huntingdon's disease, cystic fibrosis, congenital nephrotic syndromes, craneofacial anomalies, Wiskott-Aldrich syndrome, and mantle cell lymphoma.

A list of projects funded under the Quality of Life programme supporting research into orphan medicinal products is attached as Annex 1.

Previous to the 5th Framework Programme (FP) such research was supported within the BIOMED programme of the 4th FP. In this earlier programme, a total of 23 research projects with an overall budget of 8.65 m € have been supported. Further information on the Fifth Framework Programme is available on the web-site: <http://www.cordis.lu/life/home.html>.

1.3. The Community Action programme on rare disease

A community action programme on rare diseases, including genetic diseases, was adopted by the Parliament and the Council for the period of 1 January 1999 to 31 December 2003.³ The aim of the programme is to contribute, in co-ordination with other Community measures, towards ensuring a high level of health protection in relation to rare diseases. Specific attention is given to improving knowledge and to facilitating access to information about these diseases. Four actions are specified in this decision:

1. The promotion of the development of, and access to, a coherent and complementary European information network on rare diseases
2. The contribution to training and refresher courses for professionals in order to improve early detection, recognition, intervention and prevention in the field of rare diseases.
3. The promotion of transnational collaboration and networking between groups of persons directly or indirectly affected by the same rare conditions

³ OJ L 155, 22.06.1999, Decision No 1295/1999/EC of the European Parliament and of the Council of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003)

4. The provision of support at Community level for the monitoring of rare diseases with particular reference to clusters.

Further information is available on the web-site:

http://europa.eu.int/comm/health/ph/programmes/rare/index_en.htm

As part of the work programme in this context, 9 project proposals which come within the scope of the actions specified above have been identified with a view towards allocating grants totalling 1.2 m € to support these projects.

The projects concerned encompass inter alia, the creation of information networks, alliances of patient groups, European databases on specific diseases, and the organisation of information and institutional networks. The projects are expected to contribute to ensuring a high level of health protection in the field of rare diseases and to facilitating the availability of information on rare diseases within the European Community.

Organisation	Project Title	Proposed grant
Genetic Interest Group London, UK	Creating a European Alliance of Patient and Parent Groups for Genetic Services and Innovation in Medicine	110.000 €
Schlosspark Klinik Berlin, Germany	Muscle diseases – prototype of rare and disabling disorders : creation of a European Information network”.	128.000 €
University Medical Centre Utrecht, The Netherlands	Transfer of expertise on rare metabolic diseases in adults	120.000 €
Institut de Pathologie et de génétique de Loverval Loverval, Belgium	EDDNAL : European Directory of DNA Laboratories	85.000 €
INSERM Paris, France	ORPHANET :an European database on rare diseases and orphan drugs	220.000 €
University of Tampere Tampere, Finland	Information network for Immunodeficiencies	105.000 €
University of Ulster Coleraine, Northern Ireland	EUROCAT: Surveillance of congenital anomalies in Europe	260.000 €
EURORDIS Paris, France	Orphan Medicinal Products to the service of patients affected by rare diseases	130.000 €
Istituto Superiore di Sanita Rome, Italy	NEPHIRD : Network of Public Health Institutions on Rare Diseases	60.000 €

2. Information from Member States

Incentives available at Community level need to be supported by complementary national initiatives, particularly in areas such as fiscal incentives and national research projects. In accordance with Article 9 of the Orphan Regulation, information on measures adopted to-date has been received from 13 out of 15 Member States. Only 6 Member States have communicated specific measures taken to-date.

It is important to stress here that this information reflects the situation at the start of the entry into force of the regulation, and that as this information is updated, the input of Member States in this area can be expected to increase.

The information provided to the Commission is presented according to the information received from each Member State.

2.1. Austria

In Austria, the Austrian Drugs Act provides for the waiving of fees (e.g. for marketing authorisation or changes) for orphan drugs, which have not been authorised according to the Central authorisation procedure. In this case an official application should be made to the Austrian authorities for the activity concerned. The public health interest of the marketing authorisation application must be shown to be far greater than that of the individual applicant.

2.2. Belgium

Apart from the implementation of the Regulation and the nomination of a member of the relevant committee, Belgium has not yet taken any concrete incentive measures. A working party has been set up under the aegis of the Prime Minister to look at possible actions.

Subject to a feasibility study, Belgium therefore proposes to undertake two parallel courses of action:

- The possible introduction of an exemption (either full or partial) from national fees for marketing authorisations for orphan medicinal products;
- The possibility of taking special account of likely volumes of use during pricing and reimbursement negotiations, with the intention of arriving at contracts with pharmaceutical firms based on the most appropriate price/volume measure

2.3. Denmark

Similarly, in Denmark, reduced fees⁴ are charged for the marketing approval of orphan medicinal products.

⁴ Ministry of Health Order 123 of 22 February 2000

In addition the Danish Medicines Agency has communicated to interested parties, such as patients organisations, pharmaceutical companies and research organisations that the orphan drug regulation is currently operational. The Danish Medicines Agency already gives specific advice to both pharmaceutical companies and researchers concerning both design of clinical trials and development plans. Specific taskforces have been created nationally to ensure information about genomics and gene therapy with a special focus on rare diseases.

An operational collaboration also exists between the Centre for Rare Disorders and Disabilities and the Danish Medicines Agency.

2.4. France

2.4.1. Genomic research and Genome network projects

The French Ministry of Research has implemented certain specific measures to promote the availability of orphan medicinal products. Research and development into orphan medicinal products form part of the more extensive programmes launched since 1999 at the Ministry of Research, particularly under genomic research in the "Genome" programme. The study of rare illnesses and the development of orphan medicinal products are in fact part of a continuum ranging from genetic research identifying the causes of genetic illnesses, identification of potential targets as a result of these studies and development of orphan medicinal products on the basis of these potential therapeutic targets.

Against this background, two coordinated and complimentary projects have been put in place:

- a genomics programme aimed at supporting the major genomic research and functional genomics programmes in France (financing of FF 235 million in 2000),
- a "Genome" network in 2000 to facilitate the technology transfer from basic research to industrial applications. This network brings together partners from the public sector and industry for each project. It is financed to the tune of FF 200 million per annum, representing a total of FF 1 000 million of public funds over five years. The partners from industry in this network provide equivalent financing.

The objectives set out for 2001 include two fields of application in which orphan medicinal products are involved:

- new medicinal products (from target to candidate-molecule and validation of the active principle),
- cell therapies enabling specific therapies to be delivered, particularly in the case of rare illnesses.

2.4.2. Tax exemptions

Draft legislation is currently being considered to exempt companies developing orphan medicinal products from taxes and contributions payable by the pharmaceutical industry, to the Medical Insurance Scheme and the French Health Safety Agency for Health Products.

2.5. Germany

In Germany, there are currently two main applicable measures which can be expected to facilitate the availability of Orphan medicinal products. These measures are aimed at the simplification of the placing on the market of medicinal products for orphan diseases. In addition a specific measure to promote targeted research on rare diseases has also been introduced.

2.5.1. Rapid Authorisation

German legislation on medicinal products provides for the rapid authorisation of medicinal products of great therapeutic use. This also applies to medicinal products intended for the treatment of orphan diseases.

2.5.2. Reduced Documentation to support marketing authorisation

If it is in the public interest to bring a medicinal product onto the market because of its great therapeutic use, the documents on the analytical, pharmacological, toxicological or clinical tests carried out may be expanded on even *after* the medicinal product has been authorised, and further tests may be carried out if such tests appear necessary for a full evaluation of the product.⁵

2.5.3. Research measures

A special measure to promote research into orphan diseases has been drawn up under the Federal Government's health research programme and came into effect in December 2000. This concerns the promotion of the creation of a national network for groups of rare diseases, including, in exceptional cases, individual rare diseases. Further information can be found on the web-site address: <http://www.dlr.de/PT/>.

2.6 Italy

Italy has not introduced any specific national initiatives to promote and/or facilitate “national” research and development of medicinal products “designatable” as orphan medicinal products. However a number of initiatives in the field of rare diseases have been taken through targeted research financed by the national Health Fund⁶.

2.6.1 Research targeted towards rare diseases

Financing has been granted to a number of research projects which are conducted by research institutes (Istituti di Ricovero e Cura a Carattere Scientifico, Istituto Superiore di Sanità) and which concern potential innovative therapies for rare diseases, notably:

⁵ Para. 28(3) of the Law on Medicinal Products

⁶ Article 12(2)(a) of Legislative Decree 502/92, as amended

in 1998:

- Development of new gene therapy approaches to Tay-Sachs Disease (Istituto per l'Infanzia Burlo Garofalo, Trieste);
- New therapies for coelia disease (Ospedale Bambino Gesù, Rome);
- Biotechnology in the diagnosis and experimental treatment of Hirschsprung Disease (Istituto per l'Infanzia Giannina Gaslini, Genoa);

in 1999:

- Biological-molecular characterisation of the neuroblastoma with reference to the optimisation of existing treatments and the development of innovative therapies (Istituto Giannina Gaslini, Genoa);
- Gene therapy approaches to adrenoleuco dystrophy (Istituto per l'Infanzia e Pie Fondazioni Burlo Garofalo, Trieste);
- Rare diseases: national register and study models aimed at improving prevention, aetio-pathogenesis, diagnosis and therapy (Istituto Superiore di Sanità, Rome);
- Inflammatory, oxidative and autoimmune mechanisms in disabling diseases of the nervous system and research into new therapeutic methods (Istituto Superiore di Sanità, Rome).
- Italian National Registry on Rare Diseases (Istituto Superiore di Sanità, Rome): besides the organisation of the National Registry as a basis for epidemiological studies, the objectives include the organisation of a National inventory of orphan drugs available in Italy.

in 2000:

- Network of Public Health Institutions on Rare Diseases (NEPHIRD) funded by the European Commission. This project is co-ordinated by Italy (Istituto Superiore di Sanità, Rome) and include 15 Countries (EU and EU-associated). The main aim is to develop and implement an international network among public health Institutions, in order to produce valid and comprehensive epidemiological data on selected rare diseases.

2. 6.2. Improving the availability of orphan medicinal products

The Italian National Health Plan provides for generic ways of improving the availability of pharmaceuticals. The draft regulation on the national rare diseases network and exemption from contributing to costs, now in the process of being issued, does not provide for any particular initiatives: the current “rules” on the supply of medicinal products to patients will continue to apply. However, it would be reasonable to imagine that appropriate measures will be adopted to ensure wider availability of pharmaceuticals under the national health service.

2.7. Luxembourg

The Government of Luxembourg has not taken any independent measures to stimulate the availability of orphan medicinal products, but collaborates closely with and actively supports the Engelhorn Foundation for rare diseases, the headquarters of which is located in Luxembourg.

2.8. Netherlands

Measures taken in the Netherlands - and forthcoming measures - are based on three recommendations of the Health Research Council (Raad voor Gezondheidsonderzoek) which were presented to Minister Els Borst-Eilers of Health, Welfare and Sport.

1. Establishment of a national structure for orphan medicinal products within an existing scientific institution.
2. Giving priority, in conjunction with other European countries, to a number of rare diseases and subsequently encouraging large European concerns to direct their research effort precisely towards these priority diseases.
3. Promoting the development of medicinal products by means of tax incentives and subsidy schemes.

The Minister gave her view on these recommendations to parliament in March 2000.

An outline is given below of the policy measures taken by the Ministry for Health, Welfare and Sport. Reference is also made to promotional measures taken earlier in the Netherlands, and still in force, which are also of major significance to the development of orphan medicinal products.

2.8.1. Development of a national co-ordination structure for orphan medicinal products

Following a request from the Minister for Health, Welfare and Sport the Medical Branch of the Netherlands Organisation for Scientific Research (MW-NOW) and the Medicines Evaluation Board (MEB) have agreed to set up jointly a national organisational structure for orphan medicinal products and rare diseases. This structure is made up of a steering committee in which involved parties (umbrella organisations of a.o. patients' support groups, doctors, pharmaceutical companies) participate and a secretariat for support and co-ordinating activities.

One of the first tasks of this structure will be the collection of information on rare diseases and orphan medicinal products, an inventory of various diseases and numbers of patients in the Netherlands thus continuing and extending the work initiated by the Health Research Council and creating thereby, an inventory of research and a national and international forum for contact and exchange.

This will be followed by the co-ordination and promotion of basic and patient-related research. In this the Ministry is looking at scientific institutions, small biotechnology-based businesses and also bigger pharmaceutical companies and patients' organisations.

The new structure will be a contact point for questions concerning the European regulation and for consultation in connection with the pre-registration stage and issues concerning the central European register. The Netherlands hopes that this co-ordination and incentive organisation will give a better overview of developments in order to avoid wasting manpower and resources. In this way the Netherlands is also combining the

Community action programme on rare diseases with the development of orphan medicinal products. The aim of this action programme is to strengthen existing networks of patients' organisations and to create new networks. Indirectly this programme is also of importance to the development of orphan medicinal products. Recital 19 of the action programme states that "a programme of action on rare diseases must form part of a coherent overall policy that includes initiatives regarding orphan medicinal products which are possibly not sufficiently profitable in commercial terms and medical research".

The Netherlands also advanced this point in the negotiations on the action programme. A special role is provided for patients' organisations in patient-related research. A pharmaceutical company cannot deal with the respective disease without a minimum number of patients. For a clinical study of a new medicinal product for common diseases a company can find what it needs in many hospitals or doctors' surgeries. In the case of a rare disease, this is clearly more difficult: the number of patients is small and often it is not known how many patients are actually involved, where they live or how they can be reached. Patients' organisations can obviously play a significant intermediary role in this instance.

The Ministry for Health, Welfare and Sport has made available an annual budget of maximum HFL 1 million for this new national structure for a period of four years, after which the Ministry will decide whether to continue up to a maximum of ten years. In so doing the Minister for Health, Welfare and Sport will, as usual, assign tasks to Zelfstandige BestuursOrganen-ZBOs (independent bodies), in this case the Netherlands Organisation for Scientific Work-MW-NWO, on the basis of outlines. Some of the budget is earmarked for the establishment of the structure and the rest will go on subsidies for scientific research and awareness-building of rare diseases among patients above all.

The new structure will have an office in the MW-NWO. A steering committee will be set up to implement the above tasks, and representatives of the parties involved will be invited to participate in this body. These will include representatives of patients' organisations, doctors and researchers, representatives of the pharmaceutical industry and the Care Insurance Council.

2.8.2 Prioritising certain rare diseases in collaboration with other European bodies

The Minister for Health, Welfare and Sport will ask the new organisational structure to work together with its European counterparts and possibly with the European Committee for Orphan Medicinal Products to make an inventory of the state of epidemiological and scientific research into rare diseases in the Netherlands and in Europe and in the process to link up with activities developed as part of the Community action programme on rare diseases.

2.8.3. Tax incentives and subsidies at a national level

In the context of tax incentives the Netherlands refers to existing legal rulings for high-tech companies. An important aspect in this context, for example, is tax reductions for research and development work (R&D). This ruling offers persons liable to taxes (i.e.

company-owners) tax reductions on labour costs for their R&D workers.⁷ Parties other than companies (e.g. universities and scientific institutions) can also qualify for this reduction where their employees perform research and development work for a company. There is also the possibility of a general tax-reducing ruling for persons who are self-employed.

Experience in the initial years of this ruling has shown that a number of companies geared to developing biotechnological medicinal products will not make any profit and may even suffer losses. It is also possible to debit losses to the profits of the three previous years (retro-compensation), following which unlimited forward loss accounting applies. It might also be said in this connection that development costs often do not have to be entered in the books but can be set off directly against profits.

In the year 2000 voluntary writing-off of new laboratories built primarily for research and development work was possible to a limited extent.

In conjunction with the Ministry of Finance, the Ministry of Health, Welfare and Sport has come to the conclusion that supplementary tax incentives are not needed at present.

2.8.4. Activities of the Dutch Foundation for Care Research (ZON)

In its annual programme for the year 2000 the organisation "Dutch Foundation for Care Research (ZON)" intended to focus on rare diseases in respect of the chronically ill. The Ministry of Health, Welfare and Sport will consult ZON on how best to spend structural government subsidies already in place. One advantage of this is the integration in the short term of ZON with MW-MWO. The Ministry will also look at the financial support of scientific research and projects in the area of better provision of information. The Netherlands will advocate continuation of measures within the European Union regarding rare diseases (primarily collection of information and networking), including the new action programme in the field of public health (2001-2006).

2.8.5 Orphan medicinal products – implications for social insurance

Because of the special problem of rare diseases and orphan medicinal products, the Ministry of Health, Welfare and Sport has begun consultation with the Care Insurance Council (College voor zorgverzekeringen-CVZ) on how to regulate access to the social insurance package. It is particularly important to establish whether medicinal products which are registered via the central European procedure and have the status of orphan medicinal products can be included in the social insurance package without any further conditions. This also raises the question as to whether the (yet to be implemented) pharmaco-economic guidelines have to be applied before orphan medicinal products can be admitted to the social insurance package. Early co-ordination of the CVZ and the new organisational structure in the MW-NWO/ACBG will play an important role in this matter.

2.8.6 Subsidies and Incentives

⁷ This reduction amounts to 40% on a wage of HFL 150 000 and 13% on any higher amounts up to a maximum of 15 million per taxpayer per year. The condition for this reduction is the performance of R&D. In order to qualify for this reduction companies have to apply for a certificate from the Ministry of Economic Affairs.

As regards subsidy and incentive programmes, HFL 2 million has already been made available in the Netherlands for the programme initiated by the Ministry of Economic Affairs for innovative drug research and entrepreneurship (STIGON). In addition to contributions from the Ministries of Economic Affairs and Education, Culture and Science, there have also been contributions from the Netherlands Organisation for Scientific Research (NWO) and from various scientific institutions. This has made for a total of HFL 20 million over four years. This programme is geared towards the establishment of high-tech businesses and entrepreneurship in medicinal products for chronic and rare diseases. The STIGON programme is a continuation of an innovative drug research incentive that began in autumn 1999 for a period of four years.

The Ministry of Health will consult the Organisation for Applied Scientific Research (TNO) on whether orphan medicinal products can be included as a sub-theme in the theme of diagnostic and medication.

2.8.7 Dutch activities with respect to the Programme of Community action on rare diseases

The Community action programme on rare diseases (with a relatively limited budget of EUR 6.5 million) draws to a close at the end of 2003. This will be followed by a new co-ordinating action programme in the field of public health. The European Commission recently submitted a proposal for this new programme to the (Health) Council and the European Parliament. The Netherlands will ask that rare diseases be included in this new action programme to enable the independent national organisational structure to take advantage of activities within the European Union regarding rare diseases and also to gain access to a European network for information on rare diseases.

2.9 Sweden

The Medical Products Agency (MPA) has communicated to interested parties including patient and pharmaceutical industry organisations the information that the orphan regulation has come into force and information, including the possibility of obtaining funding, on the Programme of Community action on rare diseases (1999 to 2003). As part of this communication the MPA has invited proposals for actions which Sweden could take to support research into and development of orphan medicinal products.

2.10 Countries which have taken no specific national measures

Apart from the implementation of the provisions of the regulation on Orphan medicinal products and the nomination of a Member of the Committee for Orphan Medicinal Products, **Ireland, Portugal, Finland, Greece** have to-date taken no national measures to support research into, or the development and availability of, orphan medicinal products or medicinal products that may be designated as such.

2.11 Countries from which replies are still awaited

Replies to the Commission's request are still awaited from UK and Spain.

EC 31/01/01

Annex 1: List of Projects under the Quality of Life Programme supporting research into orphan medicinal products

Generic Activities

Structural studies on the mechanism of DNA excision repair
Ultraviolet-sensitive genetic disorders associated with defects in DNA repair and transcription
Molecular and biochemical pathogenesis of Friedreich's ataxia: search for treatments
Multidisciplinary approach to understanding the pathophysiology of the Wiskott-Aldrich syndrome towards improved healthcare
A systematic approach towards the understanding, diagnosis and treatment of CDGS, a novel group of metabolic disorders caused by defects of glycosylation
Development of a genomic DNA bank of IgA nephropathy (IGAN) patients and family members. New trends in genetics for the early diagnosis of familial IGAN
* Evolving evidence-based treatment strategies for infantile hyperinsulism using clinical, genetic and cell biological insights into a heterogeneous disease
* Coresets of outcome measures and definition of improvement for juvenile systemic lupus erythematosus and juvenile dermatomyositis
Nephrin in proteinuric diseases. Development of diagnostics, prognostic and treatment modalities.
* Molecular characterisation and identification of biological risk factors in mantle cell lymphoma
European collaboration on craniofacial anomalies
* Neuroprotection and natural history in Parkinson's plus syndromes: a clinical trial of the efficacy and safety of riluzole in Parkinson's plus syndromes
* European network for fetal transplantation

Key Action Cell Factory

Thematic network around cystic fibrosis and related diseases
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* Note that these projects are still in the negotiation phase

Development of high-throughput PNA-based molecular diagnostic systems
Pre-clinical evaluation of delivery systems for neuroprotective gene therapy in neurodegenerative diseases
European cell therapy in the nervous system