PM Rare Diseases
Programme text

ZonMw

Programme Text

Priority Medicines
Rare Diseases
and Orphan Drugs

(PM Rare diseases)

ZonMw
March 2011

Publisher's Imprint

ZonMw (the Netherlands Organisation for Health Research & Development), stimulates research into health and health care innovation

Progress requires research and development. ZonMw funds health research and stimulates the use of the knowledge developed – to help improve health and health care.

ZonMw's main commissioning organisations are the Ministry of Health, Welfare & Sport and the Netherlands Organisation for Scientific Research.

ZonMw
Laan van Nieuw Oost Indië 334
P.O. Box 93245
2509 AE The Hague
Tel. 070 349 51 11
Fax 070 349 53 58
www.zonmw.nl

Table of Contents

1. Introduction

In the WHO report of 2004, *Priority Medicines for Europe and the World: A Public Health Approach to Innovation*, rare diseases are mentioned as an area which merits special attention. The report declares that for the time being there remains an ongoing need to improve knowledge of rare diseases at a fundamentally molecular level.
Besides that, the report recommends stimulating translational research into those diseases for which fundamental knowledge does exist.

In 2004 the Ministry of Health, Welfare & Sport (VWS) commissioned an assignment via the ZonMw STIGON-Orphan Drugs Programme, to develop a programme of medicines for rare diseases (orphan drugs).
This programme proposal was executed under the auspices of the (Dutch) Steering Committee on Orphan Drugs and the advisory committee of the STIGON-Orphan Drugs programme.

The ultimate programme proposal, "*From Being Orphaned to being Cured*" ("*Van verwezen naar genezen*") was approved by ZonMw's board of directors and submitted to the Ministry of Health, Welfare & Sport in 2007. In December 2009 the Ministry approved the programme proposal and made available the necessary finance (see appendix IV – commissioning letter of the Ministry of Health).

The programme has a budget of 13,6 million Euros for the years 2009 – 2017 (see appendix V – programme budget).

2. Background and goals of the programme

The reason for paying specific attention to researching rare diseases is the fact that a great number of people suffer from a disease that does in itself occur very often. The number of rare diseases is estimated at 5000-8000[1]. According to the European definition, a rare disease is a life-threatening or chronic debilitating disease which occurs in no more than 5 out of every 10.000 inhabitants of the European Union[2]. Based on the estimate that 6-8% of the total population of the European Union suffers from a rare disease, we are talking about a population of 27-36 million patients. Estimates of the number of people in the Netherlands with a rare disease vary from a minimum of 200.000 to a maximum of 1,2 million patients. Approximately 80% of rare diseases have a hereditary component. This impact on public health is frequently underestimated.
Effective treatment is available for some rare diseases, thanks to research. In the meantime, more than 350 orphan drugs have been registered in the United States and around 70 orphan drugs in Europe. For many other rare diseases, however, the knowledge necessary for developing a treatment regime is lacking. This would, for example, imply that there is a lack of knowledge and insight into the cause of the disease and its natural course, which impedes an (early) diagnosis. Due to lack of knowledge of the disease mechanism, pretexts for finding a suitable therapy are unknown. Out of a number of diseases which have already been better researched, there is still too little knowledge available about the right medical care, pharmacological interventions, or about the under-use of medication. A structured, programmed approach is best suited to plugging these knowledge gaps in the various aspects of rare diseases.

1. Multidisciplinary breakthrough projects
Stimulating translational research will be done by funding large projects of multidisciplinary groups who have the ambition to achieve a breakthrough in therapies for rare diseases within five years. These consortia, consisting of researchers and clinicians, demonstrate mass and focus, are embedded in an international network and have a proven record of service.
There should be clear patient involvement shown in the design, execution and implementation of the research. Besides that, perspective on, or actual participation of the industry should also be there, depending on what stage the research is at in the project.
All grant applications for large breakthrough projects will be judged in one round.
In the event that in one round fewer than the anticipated number of excellent breakthrough projects are accepted for renumeration, a second subsidy round will be organised.

2. Minor booster projects
In addition, around four minor research projects will be financed which, within a maximum period of 1-2 years, will further elaborate an idea for a therapy for a rare disease towards a 'proof of principle/concept'; these projects could, for example, subsequently result in being followed up in a transnational programme or an E-Rare call.
Examples of such a programme could be:

- Researching an idea for a new therapy in a cell model or an animal model;
- Early clinical trial: minor experimental study in a hospital, eventually with patients, for the
- demonstration of a principal/concept;
- Research into the possibility of extending a treatment with a registered drug to a rare indication, for which the drug is not registered;
- Researching an application of a molecule that is *off patent* for treatment of a rare disease.

[1] http://ec.europa.eu/health/rare_diseases/policy/index_en.htm
[2] see also www.orpha.net

Grant applications for these projects will likewise be judged in one round. In the event that fewer than the anticipated number of booster projects are accepted for renumeration in one round, a second subsidy round can be organised.

3. Internationalisation and networking
This programme also stimulates networking between national and international researchers and clinicians.

⇒ **Participation in projects programme of E-Rare**
By participating in the project programme of the ERA-NET project E-Rare, Dutch researchers and clinicians will be encouraged to enter into new international cooperation, or to intensify network contacts by means of a communal research project. In the renumerated transnational projects of the Joint Call of 2009, Dutch research groups are financed out of this programme (in total 14 groups; total subsidy 1,67 M€). Dutch participation in future calls is as yet unknown.

⇒ **(Inter)national networks**
A small section of the programme budget is reserved for encouraging Dutch researchers and clinicians to form more (inter)national networks. This budget can be used to organise (inter) national workshops in the Netherlands, with the aim of promoting cooperation in the field of rare diseases. In addition, appeals can be made on this budget to finance travel and accommodation costs, for a maximum period of three months, to permit a Dutch researcher or clinician to engage in research or learn a technique in a foreign clinic or laboratory. Applications can take place on a continual basis, but should be submitted at least six months in advance.

The principal objective of this strategic research programme is to stimulate translational research in the field of rare diseases, with the developing of therapies as its ultimate goal.

3. Structure of the programme

With reference to the goals outlined, the types of projects (forms of subsidy) within the programme will be defined as follows:

1. Multidisciplinary breakthrough projects, aimed at the development of new therapies;
2. Small scale booster projects, aimed at the 'proof of principle/concept' ;
3. Network subsidies.

In the programme Rare Diseases and Orphan Drugs, use will be made of the strong points in the Netherlands re. rare diseases: the excellent quality and infrastructure of fundamental research, clinical research and the well organised patients associations. In addition, this programme will enable more extensive links to be formed between university research and trade & industry in the Netherlands.

The definition of rare diseases as outlined in the European Regulation on Orphan Drugs will be used. This states that no more than 5 out of every 10.000 inhabitants of the European Union may suffer from this kind of disease and that the disease ought to be a life threatening or chronically debilitating illness[3].

(*NB: The European Regulation on Orphan Drugs also applies to any new product of great value for any disease in which more than 5 out of every 10.000 inhabitants of the European Union suffer, but that would not otherwise come on to the market without extra effort. For this last group of diseases no project can be submitted in this programme.*)

The programme is open to research into all rare diseases which adhere to the aforementioned definition. No rare illnesses will be excluded from subsidy by this programme, unless:

- it is clear that a more frequently occuring disease is subdivided in such a way that it could be regarded as a (group of) rare disease(s) according to the definition, but is not so in the strict sense;
- for rare diseases already active drugs, registered for this indication, are at hand. An exception to this can be that there is clear indication that the submitted research application will lead to a safer or more effective or otherwise clinically superior drug;
- the development of a drug for a rare disease is already so far advanced that registration of the drug is imminent. An exception here could be a clear indication that the research applied for will lead to a safer or more effective or otherwise clinically superior drug.

Because of the intended integral and multidisciplinary approach, subsidies with a maximum scale of 3 M€ over five years are available.

In the total programme budget (see appendix V) 9 M€ is budgeted for the multidisciplinary breakthrough projects, so that at least three projects can be renumerated.

In principal, one application round will take place for the multidisciplinary breakthrough projects, depending on the quality of the applications.

[3] see also www.orpha.net

4. Programme procedures

4.1 Selection procedures and criteria

Various kinds of projects will be funded in this programme, and will be judged according to the accepted ZonMw procedures. Choice of procedure is dependent on the type of subsidy. A bottom-up approach will be the departure point of the programme.

- *Multidisciplinary breakthrough projects*

Following a publicised appeal, interested persons can draw up and submit project proposals and project ideas in the English language. These project ideas will be judged by the programme committee according to a number of criteria. As well as the general judging criteria of quality[4] , the relevant criteria of translational character, likelihood of developing a therapy, participation of patients and of industry, international positioning, applicants records and plan of action for handling internal communication will apply.
The programme committee determines assessment scales for quality and relevance.
In the event that two projects are judged equal on grounds of overall quality and overall relevance, the extent of the burden of disease of the researched rare disease will be applied as an extra criterion. In that case the project focusing on the rare disease with the highest burden of illness will be prioritised.

Translational character implies that the translation of molecular/mechanical knowledge towards a clinical application and vice versa, will be worked on in the project.
The projects should have the development of a therapy for a rare disease as their ultimate goal. Patient registries, research into clinical final outcomes, research into the natural course of the disease and the orientation of a drug in the treatment regime in this programme are encompassed by this character definition, as they deliver essential information to enable clinical studies to be carried out. Researchers should clearly indicate in their applications how likely it is, given the proposed research, that a therapy can be developed, and within what time frame it can be expected that the pharmaceutical industry will be able to take up further development of this therapy.

Participation of patients implies patient involvement in design, execution and implementation of the research and of the results.

Perspective on industry participation implies cooperation or contacts with the pharmaceutical industry (SME or larger companies).

Good international positioning implies that in addition to demonstrable publications in international scientific journals, demonstrable networks have been formed with other international researchers and clinicians in the field of rare disease(s) for which the application is submitted.

Record of applicants implies that as well as the aforementioned international positioning, it will also be taken into account how far applicants have cooperated with various scientific and clinical disciplines, patients (organisations) and industry in the past, whether they are in a position to lead a large multidisciplinary project, and if some of the results can be relinquished to other partners.
The record should not only be drawn up in the (pre)application, but will also be checked via an interview during the procedure (in the detailed phase of the application).

The programme committee selects the most suitable and most likely projects and invites the applicants to write a detailed proposal in English.

[4] See ZonMw publication 'Procedures (2002)', to download via the website www.zonmw.nl

The preliminary applications likewise give the committee the opportunity to steer the formulation of the subsidy application. Detailed proposals will be judged according to the various criteria set out above, by which use will be made of the expertise of consultants (national and international scientists, entrepreneurs and patients organisations). The programme committee takes all considerations into account and decides which projects will be renumerated. During the procedure, an interview round with the main applicants of the projects will also be held by the programme committee.

Each renumerated project will be supported by an advisory committee for the duration of its execution (see 4.3).

Budget costs for breakthrough projects
When submitting a project idea, only a total sum without further specification will be requested. In the case of a detailed grant application, a specified budget should be submitted according to the right ZonMw format; the total amount may not deviate by more than 15% from the amount set out in the project idea. ZonMw subsidy regulations[5] are applicable to this budget.
For the funding of economic activities in a project, specific supplementary conditions apply (see appendix Ia). Cooperation with international partners is also bound by certain conditions (see appendix II).

- *Small scale booster projects*

Interested parties can, following a public appeal, draw up and submit a project proposal and a project idea in the English language. These project ideas will be judged by the programme committee according to a number of criteria. As well as the general criteria for quality[6], for the booster projects the relevant judging criteria will be the likelihood of the success of the project and the applicant(s) record.
The programme committee determines the assessment scales for quality and relevance. Researchers should indicate clearly in their application why their proposed idea should be renumerated, and how *likely* it is, on the grounds of their proposed research, that a therapy can be developed. *Record of the applicant(s)* implies that the applicant(s) scientific experience has been or will be relevant to the researching of rare disease(s) and/or with the molecule to be researched.
In addition, the researcher should be able to demonstrate the existence of cooperation or contacts within the pharmaceutical industry (SME or larger companies), or a demonstrable intention to this end.
The programme committee selects the most suitable and the most likely projects and invites the applicants to write a detailed project proposal in English.
The project ideas will in addition give the committee the opportunity to steer the execution of the subsidy application. Finalised proposals will be judged according to the various criteria, whereby use will be made of the expertise of consultants ((inter)national scientists, entrepreneurs and patients organisations).
The programme committee will weigh up all considerations and decide which projects will be renumerated.

[5] See 'ZonMw subsidy conditions (2009)', to download via the website www.zonmw.nl
[6] See ZonMw publication 'Procedures (2002)', to download via the website www.zonmw.nl

- *(Inter)national networks*

Subsidy applications for the organisation of workshops or for working visits can take place continually, but should be submitted at least six months before the workshop or working visit takes place. This time period makes it possible to lay the application before the programme committee for judgement, and for the application to be processed. The programme committee will make a decision about the project via a written round, whereby the majority of votes will prevail.

4.2 Terms of Reference of the Programme Committee

A programme committee is set up according to the usual ZonMw procedure.
In addition, an advisory committee is also set up for each multidisciplinary breakthrough project.
The duties of the programme committee include:

- To implement the programme according to the approved programme proposal. The purposes of the programme, and unity and cohesion within the programme should be monitored hereby;
- Putting out appeals for the submission of research proposals which can contribute to the purposes of the programme;
- Judging project proposals by the various criteria for the purposes of the programme;
- Prioritising the proposals and laying them before the ZonMw board of directors;
- Approving the composition of the advisory committees of the renumerated multidisciplinary projects;
- Steering the progress and evaluation of the renumerated large multidisciplinary projects, and of the renumerated small booster projects by means of a progress report which each project should hand in halfway through the project and after the project ends;
- Overseeing the progress of the programme and keeping the client informed.

The programme committee consists of 11 members with a broad expertise in the field of rare diseases and orphan drugs (see appendix III). Committee members are either experts or representatives in the fields of fundamental research and clinical research, patients organisations and the pharmaceutical industry. Due to the multidisciplinary nature of the projects, it is important that the four different disciplines (fundamental researchers, clinical researchers, patients organisations and the pharmaceutical industry) are fully represented in the programme committee.
A representative from the Ministry of Welfare, Health & Sport will also sit on the committee as an observer. ZonMw[7]'s Code of Conflicts of Interest has been taken into consideration when composing the committee.

4.3 Terms of reference of Advisory Committees

Each renumerated multidisciplinary breakthrough project will be advised by their own advisory committee. The job of each advisory committee includes the supervision of and advising of an individual multidisciplinary project for translational research, in order to increase the likelihood of the project outcome actually leading to a therapy which will benefit patients. The advisory committee will itself (in consultation with the project applicants) determine how this supervision can best take place.
The secretary of the programme committee will simultaneously function as secretary of the advisory committees. The secretary coordinates the exchange of information between the advisory committees and the programme committee.
The composition of the advisory committees will consist of four to six persons with a wide expertise in the field of translational research, and with an extensive network.

Experience in the field of rare diseases and orphan drugs is desirable but not strictly necessary. The composition of the committee will be proposed to the secretary per individual member and be approved by the programme committee. The applicants of the renumerated

[7] Code Conflicts of Interest ZonMw (October 2010), to download via the website www.zonmw.nl

projects can come up with suggestions for the composition of the advisory committee. When composing the advisory committees, account will be taken of ZonMw's Code of Conflicts of Interest. Depending on the subject, members may be invited at random during the progress of the project to provide additional expertise.
Ultimate responsibility for the results and the implementation of a project lies with the project applicants; the supervisory committee has purely an advisory function.

4.4 Transfer of Knowledge and Implementation

Because various national and international initiatives exist and will be developed in the field of rare diseases and orphan drugs, a budget has been reserved for organising symposia and workshops for the exchange of information about these initiatives, and of the knowledge which will be obtained in this programme – mutually within the projects via workshops or in a more extensive (inter)national connection via symposia. These activities will take place in close cooperation with the Steering Committee on Orphan Drugs and the staff within the ZonMw programme STIGON-Orphan Drugs.
Once the three multidisciplinary projects have been renumerated, the first symposium will be organised (for planning, see table below). During this symposium, an update will be given on the state of affairs surrounding rare diseases and orphan drugs.
As well as that, the applicants of the three renumerated projects will get the opportunity to present their projects. This symposium can also be used to strengthen networks. Once the booster projects have begun, a workshop will be organised to offer all applicants of the renumerated projects the opportunity to present their projects. After two years a second workshop will be organised to offer them the opportunity to present the results of the booster projects. A final symposium will take place around five years after the commencement of the multidisciplinary breakthrough projects.

4.5 Planning

The table below provides an overview of the activities in the programme.

Activity	**Period**
Start of programme	January 2011
Breakthrough projects	
Subsidy round breakthrough projects	April 2011 – March 2012
Start of breakthrough projects	Second half 2012
End of breakthrough projects	Second half 2017
Booster projects	
Subsidy round booster projects	Spring 2012 – Winter 2012
Start of booster projects	First half 2013
End of booster projects	First half 2015
Networks	
Submission of subsidy applications	Autumn 2011 – Summer 2015
Knowledge transfer	
Symposium	Summer 2012
Workshop 1	First half 2013
Workshop 2	First half 2015
Final symposium	Second half 2017

5. Appendices

Appendix Ia – Financing of economic activities and State aid regulations

According to the ZonMw subsidy regulations, submitted projects can not lead to State aid that has to be reported to the European Commission. In the following, it is explained how this condition can be fulfilled.

Take note: it is the responsibility of applicants to investigate this and to explain why they think that they fulfil this condition.

In the following two situations there is no problem:
A. there is no State aid;
B. there is State aid, which does not have to be reported.
Both situations are explained below.

A. There is no State aid
The State aid regulations apply to measures that meet all the criteria of Article 87(1) of the EC Treaty. It must concern:
(1) a financial benefit (2) from State resources which confers an advantage to (3) a specific (4) enterprise or specific enterprises, resulting in (5) distortion of competition and is (6) likely to affect trade between Member States.

For grant applications within the PM Rare programme, the fourth condition is especially of practical relevance. An enterprise is defined as any entity engaged in an economic activity, irrespective of its legal form. An economic activity is an activity consisting of offering goods and/or services on a given market. This concerns the activity related to the subsidy, not any other activities performed by the applicant.

In case the subsidy is not intended for an economic activity and the applicant does therefore not act as an enterprise, the State aid regulations do not apply. The Commission considers that the primary activities of research organisations are normally of a noneconomic character (*e.g.* the conduct of independent R&D for more knowledge and better understanding).[8]

B. There is State aid, which does not have to be reported
If the subsidy is intended for an economic activity, the applicant qualifies as an enterprise. In most cases all other conditions of Article 87(1) of the EC Treaty are also fulfilled, so the subsidy qualifies as State aid. If this is the case, the requested subsidy can only be granted if it is exempt from the EC notification requirement.

Hiervoor zijn de volgende regelingen van belang:
1) *de minimis* rule: aid not exceeding a ceiling of EUR 200 000 over any period of three years does not affect trade between Member States and/or does not distort or threaten to distort competition and therefore does not fall under Article 87(1) of the Treaty.[9]

2) General block exemption Regulation[10]: the Regulation determines that State aid for research, development and innovation that meets certain criteria, is exempt from the EC notification requirement.

[8] See the Community Framework for State aid for research, development and innovation (2006/C 323/01), paragraph 3.1.1
[9] Based on Commission Regulation no. 1998/2006
[10] Based on Commission Regulation no. 800/2008

Firstly, an aid measure for research, development and innovation has to comply with certain ***general conditions***, which apply to all forms of aid that are covered by the Regulation.

- The Regulation shall apply only to transparent aid (Article 5) . This includes at least also aid comprised in grants.
- The gross grant equivalent of the aid cannot exceed certain thresholds (Article 6 (1)); these thresholds are considerably higher than the resources available for projects in the PM Rare programme.
- The Regulation shall exempt only aid which has an incentive effect. (Article 8).
  Aid granted to SMEs, covered by this Regulation, shall be considered to have an incentive effect if, before work on the project or activity has started, the beneficiary has submitted an application for the aid to the Member State concerned. (Article 8 (2)).

  Aid granted to large enterprises, covered by this Regulation, shall be considered to have an incentive effect if the Member State has verified, before granting the aid concerned, that documentation prepared by the beneficiary establishes one or more of the following criteria: **a.** a material increase in the size of the project/activity due to the aid; **b.** a material increase in the scope of the project/activity due to the aid; **c.** a material increase in the total amount spent by the beneficiary on the project/activity due to the aid; **d.** a material increase in the speed of completion of the project/activity concerned.

In practice, a PM Rare subsidy will at least meet the first two criteria, and in principle also the third criterion.

Furthermore, certain ***specific criteria*** apply regarding the maximum allowed aid intensity for research and development projects (Article 31). The aid intensity is the percentage of the total eligible costs covered by the subsidy. For the purposes of calculating aid intensity, all figures used shall be taken before any deduction of tax or other charge.

The aided part of the research and development project shall completely fall within one or more of the following research categories:
a) fundamental research;
b) industrial research;
c) experimental development.

The aid intensity shall not exceed::
a) 100% of the eligible costs for fundamental research;
b) 50% of the eligible costs for industrial research;
c) 25% of the eligible costs for experimental development.

These categories are defined in appendix Ib.

Given the translational character of the PM Rare programme, only the percentage for industrial research (b) may be used for PM Rare projects.

The aid intensities set for industrial research may be increased as follows:

A) where the aid is granted to SMEs, the aid intensity may be increased by 10 percentage points for medium-sized enterprises and by 20 percentage points for small enterprises[11] (Article 31 (4a));

[11] new EC definition SMEs (2003)

Enterprise category	*headcount*	*turnover*	*or balance sheet total*
medium-sized	<250	≤ € 50 mln.	≤ € 43 mln
small	< 50	≤ € 10 mln.	≤ € 10 mln
micro	< 10	≤ € 2 mln	≤ € 2 mln

and
B) a bonus of 15 percentage points may be added, up to a maximum aid intensity of 80 % of the eligible costs, if:

1) the project involves effective collaboration between at least two undertakings which are independent of each other and the following conditions are fulfilled:
   a. no single undertaking bears more than 70 % of the eligible costs of the collaboration project,
   b. the project involves collaboration with at least one SME or is carried out in at least two different Member States

   or

2) the project involves effective collaboration between an undertaking and a research organisation and the following conditions are fulfilled:
   a. the research organisation bears at least 10 % of the eligible project costs, and
   b. the research organisation has the right to publish the results of the research projects insofar as they stem from research carried out by that organisation

   or

3) the results of the project are widely disseminated through technical and scientific conferences or through publication in scientific or technical journals or in open access repositories (databases where raw research data can be accessed by anyone), or through free or open source software. (Article 31 (4b)).

For the purposes of points (1) and (2) subcontracting is not considered to be effective collaboration. In case of collaboration between an undertaking and a research organisation, the maximum aid intensities and bonuses specified in this Framework do not apply to the research organisation.

Table illustrating the aid intensities:

Enterprise category	***Maximum aid intensity***	
	Industrial research	*Industrial research +bonus percentage points*
Large enterprise	50%	65%
Medium-sized enterprise	60%	75%
Small enterprise	70%	80%

Following the Regulation, the eligible costs shall be the following (Article 31 (5)):
a) personnel costs (researchers, technicians and other supporting staff to the extent employed on the research project);
b) costs of instruments and equipment to the extent and for the period used for the research project;
c) costs for buildings and land, to the extent and for the duration used for the research project;
d) cost of contractual research, technical knowledge and patents bought or licensed from outside sources, as well as costs of consultancy and equivalent services used exclusively for the research activity;

e) additional overheads incurred directly as a result of the research project;
f) other operating costs, including costs of materials, supplies and similar products incurred directly as a result of the research activity.

NB: Within the framework of PM Rare the division of costs of ZonMw should be managed as laid down in the ZonMw subsidy regulations. A distinction is made here between:
- UMC's (University Medical Centres)/Universities (according to an agreement of the Association of Universities in the Netherlands (VSNU) and the Netherlands Federation of University Medical Centres (NFU) with the Netherlands Organisation for Scientific Research (NWO), ZonMw and the Royal Netherlands Academy of Arts & Sciences (KNAW));
- Health care promotion bodies and Specialist Knowledge institutions;
- Other Institutions.

In order to determine if the established thresholds for individual applications and the established maximum support levels are being complied with, the total amount of government funding on behalf of the supported activity or supported project should be taken into account, regardless of whether or not support is financed at a local, regional, national or community source (article. 7, paragraph 1). In this way it can be avoided that the support maximums are exceeded as a result of accumulation.

Take note: it is the responsibility of applicants to demonstrate that they fulfil all applicable existing conditions in order to be eligible for funding of economic activities; ZonMw will accordingly check this legally.

Appendix Ib – Definitions from the Community Framework for State aid for research, development and innovation (2006/C 323/01)

For the purpose of this framework the following definitions apply:

a) "small and medium-sized enterprises", or "SMEs", "small enterprises" and "medium-sized enterprises" means such undertakings within the meaning of Regulation (EC) No 70/2001, or any regulation replacing that regulation[12];

b) "large enterprises" means undertakings not coming under the definition of small and medium-sized enterprises;

c) "aid intensity" means the gross aid amount expressed as a percentage of the project's eligible costs. All figures used shall be taken before any deduction of tax or other charge. Where aid is awarded in a form other than a grant, the aid amount shall be the grant equivalent of the aid. Aid payable in several instalments shall be discounted to its value at the moment of granting. The interest rate to be used for discounting purposes and for calculating the aid amount in a soft loan shall be the reference rate applicable at the time of grant. The aid intensity is calculated per beneficiary;

d) "research organisation" means an entity, such as university or research institute, irrespective of its legal status (organised under public or private law) or way of financing, whose primary goal is to conduct fundamental research, industrial research or experimental development and to disseminate their results by way of teaching, publication or technology transfer; all profits are reinvested in these activities, the dissemination of their results or teaching; undertakings that can exert influence upon such an entity, in the quality of, for example, shareholders or members, shall enjoy no preferential access to the research capacities of such an entity or to the research results generated by it;

e) "fundamental research" means experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any direct practical application or use in view;

f) "industrial research" means the planned research or critical investigation aimed at the acquisition of new knowledge and skills for developing new products, processes or services or for bringing about a significant improvement in existing products, processes or services. It comprises the creation of components of complex systems, which is necessary for the industrial research, notably for generic technology validation, to the exclusion of prototypes as covered by point(g);

g) "experimental development" means the acquiring, combining, shaping and using of existing scientific, technological, business and other relevant knowledge and skills for the purpose of producing plans and arrangements or designs for new, altered or improved products, processes or services. These may also include, for example, other activities aiming at the conceptual definition, planning and documentation of new products, processes and services. The activities may comprise producing drafts, drawings, plans and other documentation, provided that they are not intended for commercial use.

[12] new EC definition SMEs (2003)

Enterprise category	*headcount*	*turnover*	*or balance sheet total*
medium-sized	<250	≤ € 50 mln.	≤ € 43 mln
small	< 50	≤ € 10 mln.	≤ € 10 mln
micro	< 10	≤ € 2 mln	≤ € 2 mln

The development of commercially usable prototypes and pilot projects is also included where the prototype is necessarily the final commercial product and where it is too expensive to produce for it to be used only for demonstration and validation purposes. In case of a subsequent commercial use of demonstration or pilot projects, any revenue generated from such use must be deducted from the eligible costs.

The experimental production and testing of products, processes and services are also eligible, provided that these cannot be used or transformed to be used in industrial applications or commercially.

Experimental development does not include the routine or periodic changes made to products, production lines, manufacturing processes, existing services and other operations in progress, even if such changes may represent improvements;

Appendix II – Grant applications and foreign research- and project organisations.

Conditions for grant provision in case of collaboration with a foreign research- or project organisation:

- The applicant/bestuurlijk verantwoordelijke is a Dutch organisation.
- The results are relevant for the Dutch context.

Possible combinations are shown in the table below:

Principal administrative organisation	Researchers	Execution in	Results relevant for
Netherlands (NL)	NL	NL	NL (+/- international)
NL	NL + international	NL + abroad	NL + international
NL	International*	NL + abroad	NL + international
NL in international consortium**	NL + international	NL + abroad	NL + international
NL with international organisation as subcontractor***	NL + international	NL + abroad	NL + international

* If the work is executed by foreign researchers only, this is no problem.

** The subsidy is provided to the Dutch organisation, which has an international collaboration agreement

*** The work is partly executed by a foreign organisation, which is paid through the Dutch organisation.

Appendix III – Compilation programme committee Rare Diseases and Orphan Drugs
(per 1 March 2011)

Chair
Prof. dr. H.G.M. Leufkens – Utrecht University
(pharmacoepidemiology/pharmacotherapy)

Vice-chair
Prof. dr. M. de Visser – AMC Amsterdam
(neuromuscular diseases)

Clinical researchers/physicians
Dr. C.M.A. Rademaker – UMC Utrecht / Wilhelmina Children's Hospital
(hospital pharmacist/clinical pharmacology)

Prof. dr. H. Tiddens – Erasmus MC Rotterdam
(pediatric pulmonology/cystic fibrosis)

Prof. dr. C.E.M. Hollak – AMC Amsterdam
(metabolic diseases)

Prof. dr. J.W. Cohen Tervaert – Maastricht UMC+
(clinical immunology/nephrology)

Prof. dr. A.K. Groen – Groningen University
(pediatrics/system biology)

Patient participation
K. Waas – Foundation for immune disorders

B. Reuser – Board member VSOP / former chair Erfocentrum

Representation pharmaceutical industry
Dr. D. Dijkstra – Groningen University
(pharmacochemistry/co-founder Axon Biochemicals)

J.G. Hanstede - BioFarmind

Observer
H.J.J. Seeverens – Ministry of Health, Welfare and Sport

Programme officer
Dr. H.J.J. Moonen – ZonMw

Appendix IV – Commissioning letter Ministry of Health, Welfare and Sport
(in Dutch)

Ministerie van Volksgezondheid, Welzijn en Sport

2009/33193/zonmw

> Retouradres Postbus 20350 2500 EJ Den Haag

ZonMw
t.a.v. het bestuur
Postbus 93245
2509 AE DEN HAAG

INGEKOMEN
24 DEC. 2009
Behandelen: Team I
Fotokopie: bestuur/MT0/FAC

Datum 23 DEC 2009
Betreft Programmavoorstel zeldzame ziekten en weesgeneesmiddelen

Directie Geneesmiddelen en Medische Technologie

Bezoekadres:
Parnassusplein 5
2511 VX Den Haag
T 070 340 79 11
F 070 340 78 34
www.minvws.nl

Inlichtingen bij
H.J.J. Seeverens
hj.seeverens@minvws.nl
T 070 340 7202

Ons kenmerk
GMT/tB 2973586

Bijlagen

Uw brief

Correspondentie uitsluitend richten aan het retouradres met vermelding van de datum en het kenmerk van deze brief.

Tot mijn genoegen kan ik u meedelen dat ik uw voorstel voor een strategisch onderzoeksprogramma rond zeldzame aandoeningen en weesgeneesmiddelen goedkeur en daarvoor de financiële middelen ter beschikking stel vanaf 2011. De looptijd van dit programma betreft vier jaar (2011-2014), maar met een uitloop tot 2017. Ik verzoek u de werkwijze met betrekking tot dit programma verder uit te werken en daarover in contact te treden met mijn ministerie (directie GMT/H.J.J. Seeverens).

Ik ben het eens met de keuze die de opstellers van het programmavoorstel gemaakt hebben voor precompetitief translationeel onderzoek. Ik stem ook in met het voorstel dat een deel van het budget (€ 2,1 miljoen) wordt gereserveerd voor financiering van onderzoek met partnerorganisaties van ZonMw, in het kader van het ERA-NET project E Rare. In 2009 zal ik hiervoor reeds € 100.000,- beschikbaar stellen zodat de eerste initiële betalingen aan projecten kunnen plaatsvinden. De start van die projecten is mogelijk door de voorfinanciering die vanuit ZonMw al plaatsvindt.

In aanvulling op het bovenstaande vraag ik uw aandacht voor het volgende. Ik ga ervan uit dat u de te honoreren onderzoeksprojecten per thema – zoals u in uw voorstel aangeeft – toetst aan de criteria van wetenschappelijke kwaliteit en relevantie en aan de criteria voor kosten en haalbaarheid. Omdat dit een programma over meerdere jaren betreft en pas in 2011 van start zal gaan en de inzichten in deze periode kunnen veranderen is enige flexibiliteit ten aanzien van de onderwerpen wel wenselijk. Daarnaast verzoek ik u vanaf het jaar 2012 jaarlijks voor een periode van vier jaar € 100.000 te reserveren voor activiteiten op het gebied van zeldzame aandoeningen en weesgeneesmiddelen die niet rechtstreeks gerelateerd zijn aan het programma.

Om uitvoering te geven aan dit strategisch programma stel ik in totaal € 13,6 miljoen ter beschikking. De jaarlijkse verdeling van de middelen is als volgt (conform uw liquiditeitenprognose) :

2009	2011	2012	2013	2014	2015	2016	2017
100.000	245.000	817.000	2.163.000	2.747.000	2.747.000	2.747.000	2.034.000

Voorts verzoek ik u in de eerstvolgende (voortgangs)rapportage dit programma zowel inhoudelijk als financieel op te nemen.

Tevens zijn de werkafspraken planning & control VWS, NWOP en ZonMw van toepassing.

Deze opdracht verhoogt niet de formatie 2008 en de daaropvolgende jaren. De maximale formatie met inbegrip van de zogenoemde taakstelling 2007 t/m 2011 is vastgelegd in de brief aan u d.d. 16 juli 2008 met kenmerk FEZ-U-2863989. Het bovenstaande programma moet binnen de bestaande formatie worden uitgevoerd.

Ik hoop dat ik u hiermee voldoende heb kunnen informeren en ik wens u succes bij de uitvoering van dit programma.

Met vriendelijke groet,
de Directeur-Generaal Volksgezondheid,

drs. P.M.A.M. Huijts

Directie Geneesmiddelen en Medische Technologie

Ons kenmerk
GMT/IB 2973586

Appendix V – Budget programme Priority Medicines Rare Diseases and Orphan Drugs (PM Rare)

· Project costs		€ 12.600.000
· Programme costs (management, committee)		€ 500.000
· Communication and Implementation (CIP)		€ 500.000
	Totaal	**€ 13.600.000**

Division of project costs:

· Multidisciplinary projects	3 projects of 3 M€	€ 9.000.000
· Minor booster projects	4 projects of 250 k€	€ 1.000.000
· Network grants		€ 500.000
· Contribution to ERA-NET	Joint call(s) E-Rare	€ 2.100.000
	Subtotal project costs	**€ 12.600.000**

ZonMw stimuleert gezondheids-
onderzoek en zorginnovatie

Laan van Nieuw Oost-Indië 334
2593 CE Den Haag
Postbus 93245
2509 AE Den Haag
Telefoon 070 349 51 11
Fax 070 349 51 00
info@zonmw.nl
www.zonmw.nl

ZonMw