Medical products: new and needed!

An investment strategy for research into innovative and relevant medical products

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory report *Medical products: new and needed! An investment strategy for research into innovative and relevant medical products*
Your reference : GMT/18/2931334
Our reference : I-150/SL/bp/848-D
Enclosure(s) : 1
Date : January 18, 2011

Dear Minister,

Better and more efficient care and greater labour productivity – the care sector is facing major challenges. New and innovative medical products are vital in responding effectively to these challenges. This is why in June 2009 your predecessor in office requested the advice of the Advisory Committee on Health Research (RGO) about a medical products research agenda. In preparation for providing this advisory report, the RGO (which has now been incorporated into the Health Council (GR)) has appointed a committee chaired by Prof. G.H. Blijham. In accordance with Health Council tradition, the advisory report has also been reviewed by the Standing Committee on Medicine. I am pleased to submit the final result, 'Medical products: new and needed! An investment strategy for research into innovative and relevant medical products'.

Besides a research agenda, another important component of the advisory report is a guide on how to utilise the knowledge and skills of researchers and companies in the Netherlands in developing these much needed medical products. The value that users, both patients and care providers, attach to the development of a product has been adopted as the starting point for this research agenda.

The RGO has always involved patients and patient representatives in the provision of advice, in line with the mission to give advice from a social perspective. For instance, we played an important part in setting up a previous research agenda: the 2006 Medical Biotechnology Research Agenda. However, the present advisory report represents a fundamental departure, in that patients and care providers have never before had such a central advisory role. I am particularly pleased that so many patients and care providers

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were willing to contribute to this unique process. I would also emphasise the recommendation to continue in the future to involve patients and care providers in the setting of agendas. It will indeed be necessary to do so, because while the consultations have produced a splendid agenda, some areas remain as yet unexplored. It is important to fill in these areas in the near future, with the same careful approach and with adequate support. Use may also be made of the methodology set out in this document. The method followed in this document for establishing the final priorities can also be used in future surveys.

The recommended Innovative Medical Products meta-programme is worthy of further definition. As Minister of Health, Welfare and Sport, therefore bearing government responsibility for sound and efficient care, you are appropriately placed to play a leading role in implementing this advisory report. The proposed meta-programme must both support new consultations and act as a lubricant for the innovation machine where market failure occurs. Needless to say, your fellow ministers of Education, Culture and Science and of Economic Affairs, Agriculture and Innovation will be important partners. Furthermore, private parties also have a role to play.

In order to arrive at a potent meta-programme I would advise setting up a programme committee, e.g. within the context of organisations such as the Netherlands Organisation for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (NWO), Technology Foundation STW and AgentschapNL. These organisations already embody the expertise that is needed. This programme committee will be in a position to examine the details of how the meta-programme can be shaped, and how in these difficult economic times the necessary financial resources can be acquired.

Recognising their substantial involvement, I have today also submitted this document to the Minister of Education, Culture and Science and the Minister of Economic Affairs, Agriculture and Innovation.

Yours sincerely

(signed)
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to:

the Minister of Health, Welfare and Sport

the Minister of Education, Culture and Science

the Minister of Economic Affairs, Agriculture and Innovation.

No. 2011/01E, The Hague, January 18, 2011

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The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Preferred citation:
Health Council of the Netherlands. Medical products: new and needed! An investment strategy for research into innovative and relevant medical products. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/01E.

ISBN: 978-90-5549-833-8

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Summary

Request for advice

The health service is facing enormous challenges. New and innovative medical products will be essential if we are to cope with these challenges. New medical products are important tools in the effort to achieve goals such as better care, more efficient care, and greater labour productivity. In view of this, and given his special responsibility for the Dutch health service, it is therefore not surprising that the Minister of Health, Welfare and Sport has asked the Advisory Committee on Health Research (RGO) to recommend specific points for inclusion in a medical products research agenda. In this advisory report 'medical products' are defined as: drugs, medical devices related to diagnosis and care, and tissue replacement products.

Justification

To answer the Minister's question, the Advisory Committee on Health Research established the 'Medical Products Research Agenda' committee. Firstly, this Committee examined the issue of whether the Netherlands is in any position to play an active part in the development of medical products. Given the country's achievements in basic and translational research, that would certainly seem to be the case. Yet the production of useful medical products in the Netherlands does seem to be lagging behind. This is a major justification for a Minister of Health,

Welfare and Sport to give a boost to scientific research in this field and to create optimal conditions for innovation.

It is then important to ask how we can identify the main medical products in question.

New method

In answering that question, the Committee focused on the needs and wishes of those who make use of medical products: patients and care providers. The Committee described its part in this as the 'pull'. In a way, the users of medical products 'pull' at those in the field of scientific and industrial research and development (the 'push'), to obtain products that are relevant to their needs.

Despite the fact that patients and care providers possess extensive experiential knowledge, surprisingly few of them have been asked for their views concerning the most important innovations in the years ahead. The Committee has tried to get this agenda on the table, and to assign priorities to each of the listed products.

On the basis of fifteen disease areas selected by the Committee, the desired products were identified with the aid of focus groups (in connection with the 'pull') and interviews (in connection with the 'push'). This has yielded a long list of products, together with a wealth of information on which of these are considered to be important by users. It included surprising products such as navigation systems for the visually impaired and medications to suppress the itching suffered by burns patients. Patients were then asked to draw up a 'top 3' for each disease area. The products identified in this way were then evaluated by the Committee. Criteria that patients were less well able to evaluate, such as the product's effect on labour productivity, and whether or not it might be commercially attractive, were added by the Committee. This approach resulted in an 'agenda' of prioritised medical products.

The Committee's use of this approach has led to two outcomes: a new method for setting an agenda from the perspective of users, and the beginning of creating a medical products research agenda.

The method described is new and requires a degree of refinement. Nevertheless, those involved have found it to be very useful. In the chosen setting, patients and care providers were very capable of articulating their future wishes and needs, and of arranging them in order of importance. It is vital that this 'pull' consultation should not take place in a vacuum. It should, instead, be related to available knowledge in the areas of academic research and industry (the 'push'). The final

ranking by means of a weighted scoring system also deserves wider application. This has prompted the Committee to make two methodological recommendations.

> Facilitate national consultations with the users of medical products, according to the method set out in this advisory report.
>
> Rank the results of user consultations using a scoring and evaluation system, as set out in this advisory report.

The agenda

In addition to the above-mentioned method, the Committee's approach has delivered a specific agenda of medical products. It should be noted that only a limited range of therapeutic areas and disciplines were included in the consultations ('pull' and 'push'). Accordingly, there is no mention of cancer, nor have the views of children and physiotherapists been recorded.

Partly because of the wide diversity of the products in question, the Committee feels that clustering specific products has enabled it to prepare a more generally applicable agenda. This has led to an agenda of medical product clusters:

A Regenerative medicine
For example: biological artificial kidney, skin regeneration, gene therapy for orphan diseases

B Therapy based on individual characteristics
For example: medication tailored to age, gender, blood values, genetics, etc.

C New medicinal products and devices targeting the effects of disorders
For example: products to treat fatigue, pain and itching

D Improved versions of existing medication
Mainly aimed at reducing side effects, but also at increased effectiveness

E New medicinal products and devices targeting the disorder
For example: anti-dementia drugs, products to enhance insulin sensitivity

F Early, accurate diagnosis involving less discomfort
For example: replacing endoscopy, systems for measuring existing and new biomarkers

G Patient toolkit to enhance self-management and self-reliance
For example: movement analysis, biofeedback, communication tools

H Improvement and expansion of existing therapeutic interventions
For example: an alternative to thrombolysis, types of dialysis involving fewer complications
I Home automation systems for remote care
For example: camera systems, sensor systems, interactive information systems
J Information processing systems and information exchange systems
For example: improved information systems between carers and between carers and patients, e-learning modules.

Given the great demand in government institutions for medical products in the fields of public health and infectious disease control, two additional clusters have been added to the agenda:

K New products aimed at preventing disease and promoting health.
L Improved resources aimed at preventing and treating infections.

In summary, regarding the content of the medical products research agenda, the Committee has made the following recommendation.

> In particular, prioritise research into medical products (desired by the 'pull') that takes place in the above-mentioned clusters.

'Innovative Medical Products' meta-programme

The key question remains of how best to put these recommendations into effect in the practical arena of research programming. In its search for solutions, the Committee has prepared an inventory of existing programmes and projects. Its guideline in this endeavour was "Does the research in question lend itself to the development of the prioritised medical products?" The Committee concludes that research into almost all products (and into their development) is compliant with existing research programmes. Accordingly, the Committee recommends that the above-mentioned three recommendations be implemented by making them fully compliant with these programmes. This leads on to the main recommendation of this advisory report.

Set up an ‘Innovative Medical Products’ meta-programme. This meta-programme would be superimposed over the existing research programmes and projects. It would have two purposes, firstly to help organise consultations with users and secondly to encourage research that focuses on the results of these consultations.

The meta-programme could catalyse research into medical products and their development.

Based on the Committee’s experiences, a number of additional comments can be made concerning both instruments of this meta-programme – the facilitation of consultations, and the promotion of research focusing on the results obtained by this means.

Conditions of the meta-programme

Firstly, consulting users requires a professional and independent approach at national level. Both the random selection of respondents and suggestive forms of questioning should be avoided. Consultations should therefore take place under the supervision of an independent and experienced facilitator who has no vested interest in the outcome of this exercise. One of the first tasks of the ‘Innovative Medical Products’ meta-programme is to specify the details of these conditions.

Secondly, it is recommended that a process of ‘subscription’ be used to encourage research into medical products that have been prioritised by users. This process can be divided into two routes. The first route, which is also most important of the two, enables the research agenda to be relatively easily implemented within existing research programmes. It involves signing up for additional funds from the meta-programme, to complement current resources within the existing programme. This generates an incentive to fit users’ needs into existing programmes. The second route, involving subscription for new funds, is for research into high-priority products that cannot be accommodated within the existing programmes.

Finally, the Committee recommends that the allocation of funding be dependent on two tests. Firstly, in terms of its history, composition and procedures, is the research group capable of conducting research into the desired products (group test)? Secondly, does the product to be developed have sufficient priority from the users’ perspective (product test)? Those applying for new funds must also demonstrate that the study in question really cannot be funded from within

the existing programmes, and that a financial investment is the best solution to the apparent market failure issue.

Funding the meta-programme

Who will provide funding for the 'Innovative Medical Products' meta-programme? The Committee feels that, besides the Minister of Health, Welfare and Sport, others too have an interest in – and stand to benefit from – a programme aimed at promoting the development of highly rated medical products, as outlined in this advisory report. The parties in question include the Ministries of Education, Culture and Science (OCW) and Economic Affairs, Agriculture and Innovation (EL&I), health funds and patient organisations, existing public-private partnerships, and the health industry. This leads to the following recommendation.

> Convince all stakeholders of the importance of joint funding for the 'Innovative Medical Products' meta-programme.

Clearly, the ambitions set out in all these recommendations cannot be realised without a considerable financial effort. It is equally clear that the benefits in terms of health gains, accessibility and affordability fully justify such an effort.

Dialogue

The 'Innovative Medical Products' meta-programme focuses on products that emerged from consultations with users and subsequent prioritisation by experts. This 'pull' approach is a new and vital addition to the 'push' on product development generated by the research and development field (academic world and industry). However, there is also a limitation. Users are not always aware of revolutions still concealed within the laboratories and research departments of 'push' parties. A regular dialogue between users and researchers/developers should help to ensure that any potential products based on this work are not lost. This leads to the final recommendation.

> Regular dialogue meetings should be held between 'pull' (users) and 'push' (researchers and developers) within the 'Innovative Medical Products' meta-programme, with the aim of gaining early insights into product development in the longer term.

Chapter 1

Introduction

1.1 Request for advice

The healthcare sector is facing major challenges. New and innovative medical products are vital in responding effectively to these challenges. Better care, more efficient care, greater labour productivity: new medical products are important tools for achieving these objectives. In view of the above, and of his special responsibility for Dutch healthcare, it is not surprising that the Minister of Health, Welfare and Sport has requested the Advisory Committee on Health Research (RGO) to provide its advice on the possible form of a new medical products research agenda. The present document answers this request.

The Minister's request has three constituent parts, each of which has its own chapter in this document. In brief, the three constituent questions are as follows.

1 What legitimate reasons are there for investing public resources in medical products research?
2 Based on this justification what specific form should an incentives agenda for research into medical products take?
3 How might an agenda of this kind best be translated into specific actions?

In other words, the Minister asked about the why, what and how of public incentives for research into medical products. He also asked for account to be

taken of the international context, and expressed interest in how the agenda could be kept up-to-date in the course of several years (see Annex A).

The request for advice describes medical products as pharmaceuticals, medical devices and biomaterials. The Committee has observed that these terms may lead to questions and misunderstandings. This document therefore uses the alternative terms pharmaceuticals, medical devices for diagnosis and care, and tissue-replacement products.*

1.2 Working method

In preparation for the advisory report, the RGO appointed a committee, chaired by Prof. G.H. Blijham, known as the Medical Products Research Agenda Committee (see Annexes B and C, respectively, for the composition of the RGO and the Committee).

The advisory report is presented in the form of a triptych. The left panel (Chapter 2) is concerned with the 'why' question, i.e. the justification: why should the Ministry of Health, Welfare and Sport invest in research? The centre panel of the triptych (Chapter 3) forms the broad foundation of the advisory report, and deals with the 'what' question: what products deserve to be on the research agenda? Finally, the right-hand panel (Chapter 4) addresses the 'how' question, i.e. implementation: how should the Ministry of Health, Welfare and Sport facilitate and encourage research into and the innovation of medical products? Finally, Chapter 5 sets out the recommendations to the Minister of Health, Welfare and Sport.

The 'why' question

In answering this question the Committee assumed that an active medical products development climate in a given country means that these products would become available for patients sooner. Substantiating this assumption would require international comparative research, for which the Committee had neither the time nor the methodology. However, the question remains as to whether this development climate is served by public incentives. Two avenues were explored in answering the question.

* See Annex F for definitions of these terms.

Firstly, the Rathenau Institute mapped out the state of health research in the Netherlands in relation to the rest of the world. This investigation was to ascertain whether the state of health research would justify targeted product development incentives. The second avenue involved analysing case histories. To this end, Technopolis BV has described how the six cases given in the RGO advisory report entitled *Grinding links* (which addressed product innovation in the care sector, as viewed from the triple perspective of care-science-industry) have fared since the document was published in 2002. The collective findings give rise to the three considerations that justify related research incentives in selected fields by the Minister of Health, Welfare and Sport.

The ‘what’ question

The considerations that justify incentives for research into new medical products do not lead automatically to a specific agenda. The process of answering the ‘what’ question determines which products should be involved. We opted for the user perspective. What needs for medical products are felt by patients and care providers, how can they be defined, and how can they be prioritised in the light of the government’s social challenges? The Committee was accordingly required to develop a new method for setting research agendas and priorities. This part of the triptych therefore leads to conclusions concerned not only with the outcome (a medical products research agenda) but also with the method needed to get there.

The ‘how’ question

Given that public incentives for medical products research can be justified, and a method is available for determining which products are involved, the question that remains is how best to shape these incentives. Concerted effort on the part of researchers, developers and users would appear to be an important success factor. Five case studies were examined in order to shed light on this area. Each of these cases was the initiative of an outside party. The academic researchers were behind the partnership and innovation for the HOVON case, while for the Duchenne Parent Project case, it was the young patients themselves, and their parents. A health fund (funding body, the Dutch Kidney Foundation) was behind the Implantable Artificial Kidney case, while industry was involved in the Philips case, and the government in the HAART case. The contours of an incentive programme were outlined, based on the experience gained, and on an analysis of the current partnerships in Dutch medical research.

Users (patients and care providers), researchers (from the academic world and industry) and several others, (e.g. public sector and funding bodies) participated in a reflection meeting on the creation process and the content of the research agenda. This meeting was also tasked with making suggestions for implementation. The final advisory report was reviewed by the Standing Committee on Medicine of the Health Council. The RGO subsequently adopted the advisory report.

1.3 What is the scope of the research agenda?

Although the research agenda has a broad scope (all medical products: pharmaceuticals, devices for diagnosis and care, and tissue-replacement products), it also has limits.

Firstly, the agenda is concerned with medical products and the research that leads to their development. This means that other health research of great public relevance is excluded from this agenda, e.g. research into care sector organisation, into medical treatment that does not involve products, and into the sociopsychological effects of disease. As part of the advisory phase, patients themselves confirmed that medical products by no means always rank among their most urgent needs.

Secondly, the Committee was obliged to be selective, given the limited time and resources available. For instance, the Committee opted to use fifteen disease areas as a base. Although several disease-transcending clusters emerged in the analysis, it cannot be ruled out that the way the disease areas were chosen has eliminated important products or clusters.

Finally, the Committee considers that listing user needs has produced so much of value that everyone should be able to utilise this resource as they see fit. The data were analysed for this document from the perspective of the Ministry of Health, Welfare and Sport, while endeavouring to provide the Ministry with usable guidelines. However, other social parties will be able to use the agenda from their own perspective, while basing their choices on their own analysis. Furthermore, as stated above, the agenda needs to be worked out in greater detail with respect to disease areas other than the fifteen the Committee selected. The agenda is therefore a work in progress, and is intended to encourage everyone to set to work with the data from their own perspective.

1.4 Guide for the reader

As stated above, the advisory report is presented in the form of a triptych. The 'why', 'what' and 'how' questions are discussed and answered in sequence: the Committee's activities and analyses. Then in Chapter 5 come the RGO's recommendations to the Minister of Health, Welfare and Sport.

The annexes have all the relevant background information, such as: the request for an advisory report (A); the members of the RGO (B) and the Committee (C); the experts consulted (D); and the participants in the reflection meeting (E). Annex F is a glossary of terms. Annex G presents the details of the methodology used by the Committee to arrive at the content of the research agenda. Annex H is a summary of the relevant aspects of the national and international context in which the knowledge institutes and industry operate, as these affect a medical products research agenda (obtained from the interviews and relevant reports). Finally, Annex I presents the extensive SWOT analyses of the various cases from Chapter 4 (the 'how' question).

Apart from the present document, there is also a background document, 'Medical products: new and needed! Background studies for the investment strategy for research into innovative and relevant medical products', which includes three background studies.[1] The first is from the Athena Institute of VU University Amsterdam, which focuses on the medical product needs of patients and care providers. The second is from the Rathenau Institute in The Hague, which describes health research funding and output. The third background study produced by Technopolis BV is the follow-up of the cases given in the 2002 RGO advisory report entitled *Grinding links*.

Chapter 2

Justification of medical products research (the ‘why’ question)

2.1 Introduction

Public funding of research and development (R&D) by the Ministry of Health, Welfare and Sport requires clear justification now and in the future, as the Minister states in his request to the RGO for an advisory report. This justification must be based on the public interest in developing innovations and the market situation in which private parties operate. The Minister requests the RGO to recommend criteria to be used for identifying research areas in which public funding and control by the government are justified. The present chapter answers this question.

2.2 Method

In answering this question the Committee assumed that an active medical products development climate in a country means that the products concerned would become available for patients sooner. Substantiating this assumption would require international comparative research, for which the Committee had neither the time nor the methodology. Furthermore it would appear that factors other than the scale and quality of the research concerned, such as the health insurance system, the regulations and the wealth of the country, also play important roles. A cause-and-effect relationship between research into new medical products and the speed with which these can be implemented is

therefore difficult to establish. Accordingly, the Committee elected to interpret the Minister's question about justification as follows: what criteria are relevant in a general sense as justification for a public effort to encourage research into new medical products using public funds?

The public duties of the Ministry of Health, Welfare and Sport were the starting point for answering the Minister's request for an advisory report (Section 2.3). In order to provide a more in-depth answer, the Committee first sketched out the characteristics of scientific research in the Netherlands, focusing on health research and – as far as possible – medical technology (Section 2.4). The Committee then studied the innovation process and the possible role of the government, with reference to several cases that were previously raised in the RGO advisory report entitled *Grinding links*[2] and updated for the present advisory report (Section 2.5). Based on this analysis the Committee defined three criteria to identify the research activities for medical products worthy of a place on a research agenda (Section 2.6).

2.3 The Ministry of Health, Welfare and Sport serves a public interest

The ambition of the Ministry of Health, Welfare and Sport is to keep everyone healthy for as long as possible and to help those who are ill to recover as quickly as possible. The Ministry also seeks to support disabled people and encourage social participation. In addition, the changing demand for care, and the consequences for labour productivity in the care sector, must be catered for. Finally, the Ministry wishes to keep care affordable. These ambitions are expressed in the Public Duties for Public Health and Healthcare.[3] Medical products research and innovation are likely to contribute to this mission. Herein lies part of the Ministry of Health, Welfare and Sport's justification for supporting research efforts of this kind. Any additional conditions that have to be met are addressed below.

2.4 Outline of health research in the Netherlands

2.4.1 Quantity and quality of health research in the Netherlands

When examining the quality of medical and biomedical research in the Netherlands, the Committee pursued two avenues of investigation . The RGO engaged the Rathenau Institute to perform a bibliometric analysis to develop a profile of the Dutch research effort. This in turn would provide a context within which to establish the position of medical and biomedical research (for the

details of entire analysis see the Rathenau Institute background study[1]). An examination was also made of the results of impact analyses on the medical and biomedical research performed by the Centre for Science and Technology Studies (CWTS).[4] The latter work was carried out under the auspices of the Dutch Federation of University Medical Centres (NFU).

The bibliometric analysis places the total Dutch scientific output in an international perspective. Figure 1 shows for each field how the scientific output in the Netherlands relates quantitatively to the other countries that perform research in the field concerned. The size of the circles indicates the magnitude of world-wide output. The colour codes identify the sector of the research field in question: green is for medical sciences. Unfortunately it was impossible to distinguish the medical sub-disciplines within the engineering and natural science subjects.

Figure 1 shows the degree of specialisation on the y-axis. An above-average degree of specialisation (>100) means the Netherlands publishes a greater quantity, in proportional terms, than the rest of the world in the field concerned. A high concentration (plotted on the x-axis) means that relatively few countries are active in the field concerned. A high degree of specialisation coupled with a high concentration (the top right quadrant) therefore means that those in the field concerned, in the country in question, publish a large amount internationally in relative terms, and also that they have relatively few international competitors. Placing the various circles with their specific sizes in the quadrants produces a profile of the international research position of the Netherlands in each field.

It appears that the Netherlands has a strong medical profile in scientific research (Figure 1). In general, it may be concluded that Dutch researchers in the medical domain publish more material than average (quantitatively) in an international perspective and that they rank highly against their international competitors (also in quantitative terms).

It goes without saying that this does not apply exclusively to research into medical products. More to the point, some medical disciplines are entirely unrelated to medical product innovation, as is the case for health services research. Unfortunately it was impossible to distinguish between medical research into medical products and other medical research. Nonetheless, the Committee considers the Dutch research profile to be promising not only for medical research, but also for medical products research. This assumption is supported in the bibliometric analysis performed on behalf of the Royal Netherlands Academy of Arts and Sciences (KNAW) into the regenerative

medicine multidisciplinary research domain. KNAW has revealed that the Netherlands contributes an average of 3% to worldwide regenerative medicine output, while this country's average contribution across all fields is 2.5%.[5] Accordingly, a multidisciplinary field that is oriented to the development of medical products, also displays a relatively high (quantitative) level of scientific output.

No figures categorised according to subdisciplines are available for the engineering sciences, e.g. for medical technology. However, the three technical universities in the Netherlands have established a clearer life sciences and medical technology profile in recent years.[6] For instance, partnerships have been formed in various parts of the Netherlands, such as Medical Delta (in the west of the country); Health Valley (in the east); and LifeTec Network (in the southeast). Furthermore, eight Centres of Research Excellence (CoREs) have been formed within the Netherlands Organisation for Scientific Research – Innovative Medical Devices Initiative (NWO-IMDI) programme. These are but a few examples pointing to an increasing medical technology focus within technological research in the Netherlands. The high quality of technological research in the Netherlands is apparent from a separate bibliometric study performed by the Netherlands Observatory of Science and Technology (NOWT), which reveals disproportionate activity in biotechnology, genetics & heredity, medical informatics and imaging (including neuroimaging) in the Netherlands in comparison with sixteen reference countries. In the case of medical informatics (second place in the group of selected countries) and imaging (fourth place), the Netherlands has a substantially higher citation impact than the reference countries.[7] Analysis of the Dutch patent position produces the same research priority areas with conspicuously good scores in medical informatics (twice the global average) and imaging (four times the global average), which is aided by the presence in the Netherlands of strongly innovative companies in the field.[8]

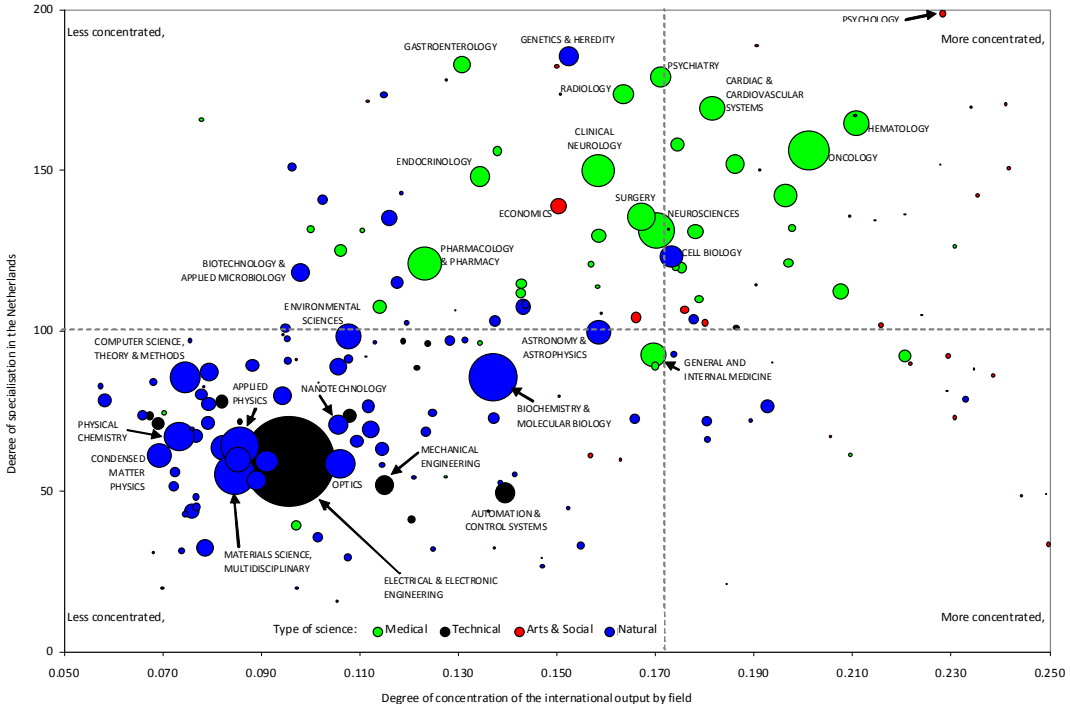

Figure 1 The output of Dutch medical sciences (in quantitative terms) is relatively large (degree of specialisation). It also enjoys a favourable position in terms of international competition, in a quantitative sense, due to the relatively high degree of concentration involved. The x-axis shows the concentration: a measure of the number of countries performing research in the discipline concerned. The higher the concentration, the fewer countries that perform research in the field concerned. The y-axis shows the degree of specialisation: a measure of the relative output of the discipline concerned. The higher the degree of specialisation, the larger the output relative to the global average. The size of the circles is a measure of the size of the field concerned. The medical disciplines are shown in green, the technical disciplines in black, the arts and social sciences in red, and the natural sciences in blue. It was impossible to distinguish medical subdisciplines within the nonmedical disciplines. See also the background study.[1]

The observation about the scale of medical and biomedical research in the Netherlands corresponds with the analyses performed on behalf of the NFU on the scientific output of the UMCs.[4] Besides quantity, these analyses also addressed the quality of scientific research. There are two striking conclusions. Firstly, approximately one third of the total scientific output of the Netherlands is clearly linked to research in the eight UMCs, and is therefore oriented to life sciences and clinical medicine. This confirms the picture that emerged from the Rathenau Institute analysis. Secondly, these publications have a considerable international impact. An analysis of the citation frequency of scientific

publications shows scores for Dutch medical and biomedical publications far above the global average. According to the NFU analyses, Dutch medical and biomedical publications are not only characterised by sheer quantity at the national level , they also have a reputation for high quality at international level.

Table 1 List of citation scores, based on the NFU publication 'Wetenschap gewaardeerd (Science valued)'.[4]

Assessed unit	Citation score[a]
All publications worldwide	1.00
All publications of the UMCs	1.40
All publications from the Netherlands (including UMCs)	1.34
All Dutch clinical medical science publications (including UMCs)	1.29

[a] An update of the figures for 2007 and 2008 doesn't significantly change the overall picture.[7,9] The citation score is equal to the amount of the international output by field of citations divided by the average amount of citations for all publications in that research field. A leading publication has more citations, i.e. the citation score is a measure of quality.

Thus, not only is Dutch medical and biomedical research carried out on a relatively large scale, its quality is also excellent. This analysis is supported by the Netherlands Observatory of Science and Technology (NOWT).[7]

The reasons for the substantial quantity and high quality of medical and biomedical publications are open to speculation. Is it the traditionally ample research funding (albeit relative to other disciplines, not to other countries[10])? Might it be due to the effective collaboration of preclinical and clinical research through the physical and organisational proximity of universities and university hospitals? Is the Netherlands simply too small a country for large-scale infrastructure for engineering? Might the major role of the health funds in financing health research be responsible? A more detailed analysis of these possible causes is outside the scope of this report. It is important to emphasize that the Netherlands scores very well indeed in terms of the size and quality of its health research, and that this gives it a solid scientific foundation for the development and testing of new medical products.

2.4.2 *The Dutch government's role in shaping health research*

In the context of the justification question, also the answer to the following question is relevant: is the Netherlands' prominent national and international position in medical and biomedical research partly due to strong central government control (i.e. the allocation of public funds earmarked for scientific research in a specific area of research)? This can be answered by determining

whether the Dutch government does in fact shape research and, if so, whether it is this that has boosted the quantity and quality of research in this country.

The Rathenau Institute also investigated this point in its survey of the Dutch situation (see the background study[1] and Figure 2). In summary the point is that there are few controls on public funds for health research and research infrastructure, which the ministries largely dispense in the form of unrestricted basic funding (government funding). Until 1995, this was the budget of the Ministry of Education, Culture and Science for the universities. In 1995 the budget of the Ministry of Health, Welfare and Sport for the university hospitals was transferred to the Ministry of Education, Culture and Science. This explains the sharp rise in unrestricted basic funding in that year. At some times the effect of a targeted investment in a given clearly defined research theme is evident (thematic competition through the Netherlands Organisation for Health Research and Development (ZonMw)/Netherlands Organisation for Scientific Research (NWO); indirect funding mechanism). Since 2002, natural gas revenues have been invested through the Economic Structure Strengthening Fund (FES) and the Knowledge Infrastructure Investment Subsidy Scheme (BSIK, formerly ICES/ KIS-3). The recipients included the Netherlands Genomics Initiative (peak 2002), and, later on, consortia such as Top Institute Pharma, the Centre for Translational Molecular Medicine (CTMM) and the BioMedical Materials Programme (BMM). This form of funding has increased in the past ten years. It gives the government an opportunity to invest in selected themes, and thereby to exercise thematic control. The focus also ensures economic valorisation in these kinds of consortia for guidance towards short and medium-term research objectives. However, it is still the case that health research and the research infrastructure are largely free of thematic control by government.

This observation does seem to create a paradox, in that the situation perceived by many researchers is quite different from the reality, which involves a near absence of control. Indeed, their perception is that there is a relatively high degree of control, and that this has tended to increase rather than decrease over the past twenty years. This is probably a consequence of government management of the process, with an emphasis on quality, focus and mass. Accordingly, far more than ever before, universities and UMCs engage in the thematic allocation of research money to specific focus areas and excellent groups.[11] The same occurs in the Netherlands Organisation for Scientific Research (NWO)/Netherlands Organisation for Health Research and Development (ZonMw), while health funds also operate in a more programme-

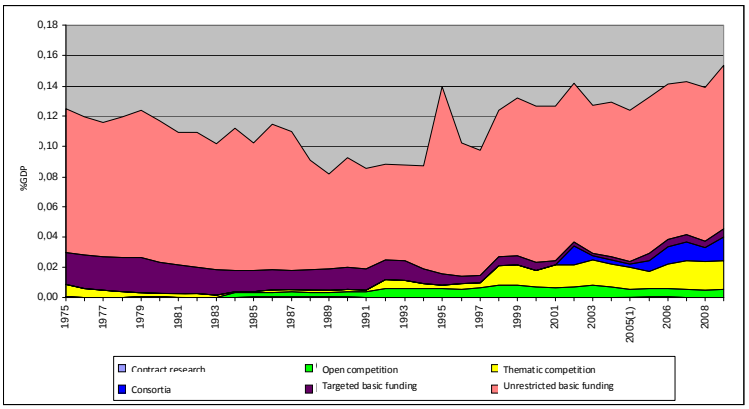

Figure 2 Funding forms for medical research as a percentage of gross domestic product (GDP) for 1975-2009.

based way. Furthermore, the requirement to match major external sources of funding, such as the FES projects, with internal financial resources is increasing the need to assert thematic control at the level of the knowledge institutes.[12] In other words, this involves replacing freedom of research in a relatively protected environment with the need to respond to the opportunities that present themselves in an extremely competitive environment. The explanation for the paradoxical perceptions of researchers is that although relatively little actual thematic control is asserted by the government, there is a degree of process-related management. This entails considerable thematic control by the knowledge institutes and funding bodies themselves.

Are there any visible benefits in those cases where the government does use thematic management? It is difficult to answer this question, but there are definite signs that this approach has the potential to deliver useful results.

In 2007, the RGO expressed its views on this theme in the advisory report entitled 'Research that counts. The responsiveness of university medical centres to public health and healthcare issues'.[11] The RGO then concluded that the UMCs were generally sufficiently sensitive to society's needs and views to uphold a balanced and socially relevant research programme.

It has been demonstrated that government thematic control can help in fields such as psychiatric research and rehabilitation research. The academisation of these disciplines has been greatly boosted by the availability of funds in thematic programmes at the Netherlands Organisation for Health Research and Develop-

ment (ZonMw) (namely '*GeestKracht*' and 'Rehabilitation Research'). '*GeestKracht*' started in 2001 and is scheduled to terminate in 2011. Consequently the programme has yet to be evaluated, but a clear improvement in research output and quality is already apparent. Indeed, as Figure 1 shows, the Netherlands has a high level of psychiatric research output (high degree of specialisation). The first programme (Rehabilitation Research) has now been completed and evaluated, and a second programme (2006-2010) is in the final phase. The evaluation of the first programme has shown that, after eight years, rehabilitation research is embedded in the UMCs and rehabilitation centres, and that socially relevant and high quality rehabilitation research has been promoted.[13,14] These two examples show that government thematic control and the responsiveness of the research institutions are able to improve the scale and quality of research.

2.4.3 *Translational research in the Netherlands*

The analysis in Sections 2.4.1 and 2.4.2 is concerned with the total picture of health research in the Netherlands, so it draws no conclusions about research into medical products as such. The step from fundamental health research to applications depends on translational research. The boundaries between fundamental research and translational research are not always sharply defined, as shown by the RGO definition*. The process will usually be iterative in nature.

The RGO produced the report 'Translational research in the Netherlands – From knowledge to clinic' in 2007.[15] The report's findings can be summarised as follows: the Netherlands currently occupies a strong position in translational research, but there is no guarantee that it will retain this position. The RGO recommendations seek to safeguard the conditions for success in the future, while eliminating obstructing factors as far as possible. The most important success factors are: the strong interaction between medical faculties and university hospitals in the UMCs; the availability and educational standard of clinical researchers; and the existence of high quality cohort biobanks.

In recent years, the government has used FES funds to make additional investments in translational research, resulting in the 'Top Institutes' TI Pharma, CTMM and BMM. Here, public and private sector partners come together to actively support multidisciplinary research. Translational research has also received considerable attention from other funding bodies, such as the

* The RGO considers translational research to be a phase in the knowledge chain, comprising all the steps from identification (in patients or patients' material), through diagnostic leads, prevention and therapy, to early clinical application in practice. Research questions may arise from either clinical practice or the laboratory.[15] See also Annex F.

Netherlands Organisation for Health Research and Development (ZonMw) and the health funds.

2.4.4 Summary

In addition to being strongly oriented towards medical and biomedical research, the Netherlands' research profile can lay claim to scientific output of a very high standard. This situation, which was achieved without strong government thematic control, relies largely on thematic choices made by the knowledge institutes themselves. Nonetheless, government thematic control has definite potential benefits for the scale and quality of a research field.

Translational research is also of high quality in the Netherlands. It is part of the body of medical and biomedical research, and is vital to the translation of fundamental medical and biomedical knowledge into applications, in the form of medical products. It is because the Netherlands has no guarantee that it will retain this advantageous position, that the government has invested substantially in the form of public-private Top Institutes.

The Committee therefore concludes that an essential part of the knowledge base is adequately safeguarded, and this is a substantial element of the justification.

2.5 The performance of the Dutch innovation system

The Committee demonstrated in Section 2.4 that health research in the Netherlands is performing well. While a large volume of excellent knowledge has been accumulated in the Netherlands, this has not led to the development of as many innovative medical products for the care sector as might be expected. This situation is referred to as the knowledge paradox.[16,17]

The Netherlands scores well in terms of many innovation indicators, such as trademarks, companies with national and international joint venture partners, and education. Conversely, some indicators score below average for a member state of the EU-27 and the OECD. These include the public R&D budget for health, patents, and company investment in R&D and innovation.[10,18] Accordingly, there is definitely room for improvement in the strength of Dutch innovation and in the translation of knowledge into medical products, for example.

A better understanding of the innovation system is needed to clarify the knowledge paradox and to respond to the Minister's request for justification. The relevant explanation is given in this section.

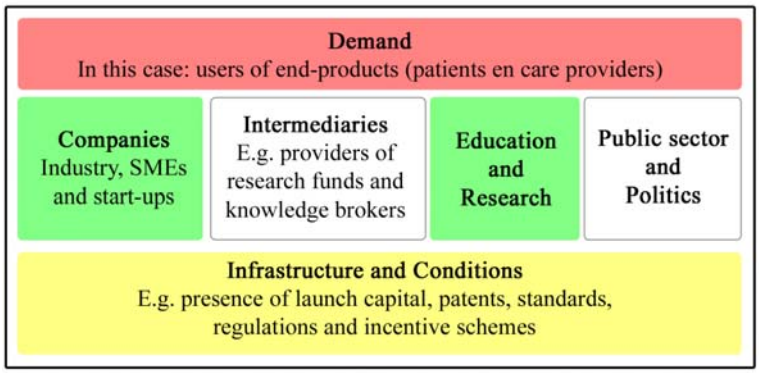

Figure 3 The various components of the innovation system.[19] The constant mutual influence of these elements affects the direction and pace of innovation. The users of innovations, which are referred to in this document as the 'pull', are shown in red. The most important knowledge suppliers and developers, which are referred to in this document as the 'push', are shown in green. The infrastructure and conditions are shown in yellow. These are often at the centre of an ongoing debate concerning obstacles and the knowledge paradox.

The innovation system (Figure 3) is a diagram of the environment in which the innovation process takes place. This environment consists of various elements whose constant interaction affects the direction and pace of the innovation process in many different ways.[19] Innovation is therefore a collective process, in which components may variously facilitate or obstruct an innovation.

The 'innovation system' concept can be applied at many levels of abstraction. For instance, the 'Dutch innovation system' refers to the entire national innovation system, and 'regional innovation systems' refer to such things as Health Valley in the east of the Netherlands, LifeTec Network in the southeast of the country and Medical Delta in the Zuid-Holland region. People usually associate the breakthrough factors for a specific new technology with technological innovation systems. These systems have fewer players, making it easier to identify the networks of players involved.

Section 2.3 shows that fundamental and translational research in the Netherlands is performing well. Nonetheless, there is insufficient translation into relevant new products for the care sector. This has a direct bearing on the importance of public health in the Netherlands. Products that are beneficial to the duration or quality of life become available too late, if at all, and products that are important for the effectiveness and productivity of care providers fail to materialise. As

Figure 3 shows, many reasons can be put forward to account for this, such as a poor match between scientific research and the industrial sector, and excessively strict regulations for testing and admitting new products. These factors are now coming under scrutiny, in contexts such as large public-private partnerships and by amendments to regulations.

The need to shed light on factors that obstruct or promote successful innovation in the medical domain has prompted a fresh look at the RGO advisory report entitled *Grinding links*. The attached background document contains a follow-up study of the six cases involved.[1] The obstructing and promoting factors that emerge are shown in Boxes 1 and 2.

The factors that act as catalysts and impediments in Boxes 1 and 2 clearly show that there is the potential for interventions to improve the progress of key innovation system processes. The government has various tools at its disposal for applying interventions of this kind, such as legislation and regulation; the provision of funds; and the facilitation of network building. Some of the above is also applicable to implementation of the medical products research agenda; the related 'how' question is revisited in Chapter 4.

Nonetheless, the question that remains is whether the public need for new medical products is sufficiently served with these factors. Even if these factors are tackled effectively, the risk remains of a poor match between care sector demand and product availability, which is referred to as market failure. The Committee expresses this notion as an insufficient match between push* (the knowledge and product development of knowledge institutes and industry) and pull** (the needs of patients and care providers). In this advisory report, the RGO thus defines market failure as a situation in which, for various reasons, industry does not automatically undertake the development of a product , resulting in a mismatch of supply and demand. Indeed, the WHO too has found that there is a mismatch between supply and demand for medical devices.[21]

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* The Committee defines push as the knowledge producers and developers, which constitute 'education and research' and 'companies' in the innovation system.

** The Committee defines pull as the end-users and other users of medical products, which constitute 'demand' in the innovation system. In a practical sense these are usually patients and care providers. There is an area of overlap, in which players are part of both the pull and the push. See also Annex F.

Box 1 Catalysts in the innovation process

- Clear direction in the search process: medical products that make a difference between life and death, which therefore have the potential for major health gains, will be developed faster because all parties are motivated to make products of this kind available.
- Heterogeneous network building: the involvement of patients and patients' organisations ensures a good match of supply and demand and is important for the success of innovation. Products that people really need will be far more successful than those that are marketed without due thought.
- Countering resistance: patients are more than capable of contributing their thoughts on issues of reimbursement, and they can even be of overriding importance in this regard.
- Availability of financial funds: e.g. the orphan medicinal products policy rule and the, now ended, BioPartner programme that was operated by the then Ministry of Economic Affairs.
- Experimenting: the willingness of involved parties to take an unconventional approach and to engage in give and take in order to achieve the desired result as rapidly and effectively as possible.
- An effective infrastructure: an infrastructure without barriers and with short lines of communication is beneficial to network building.
- Favourable constraints: legislation and regulations can benefit key processes. For instance, extending patent law for orphan drugs has been beneficial in terms of market creation.

Box 2 Impediments in the innovation process

- A small market: products for minor disease areas are often relatively expensive to develop, because it takes longer to recoup the development investment compared with products that have a large market.
- Little scope for experimentation: the Netherlands is a small country. This means that certain types of research are relatively difficult to perform, possibly because there are too few patients. Also a lack of large investors impedes the commercialisation and production of medical products.
- Unfavourable constraints: legislation and regulations can impede key processes in the innovation system. The Netherlands has a reputation for strict adherence to laws and rules, resulting in procedures taking longer than they do in other countries. Furthermore, whole areas of research sometime have to be moved abroad as they are banned in this country. One example of this is clinical research in children. The Committee for Medical-Scientific Research Involving Minors (also known as the Doek Committee) reported that the Netherlands has stricter regulations in this area than surrounding countries.[20] Other examples are the public participation and objection procedures in the Netherlands for permits for releasing genetically modified organisms into the environment. Procedures of this kind, which are unique to the Netherlands, make the entire process much more protracted.
- Unclear constraints: disagreement about the effective demonstration of efficiency, on which decisions about reimbursement are based, or a possibly excessively high price for a new medicine that is at risk of not qualifying for reimbursement.
- Funding shortage: a lack of funding for large-scale clinical studies, which are a necessary step from fundamental/translational research to the market for biotechnological medical products.
- Insufficient exchange of knowledge: a lack of reciprocal knowledge transfer between the medical and technological worlds.
- Inability to give direction: if people are not prepared to tackle a given problem, or to take responsibility for a difficult, critical step, then the development of a product will stall (because no-one has taken ownership of the problem).

With regard to the innovation system, the Ministry of Health, Welfare and Sport's investment in research is justified precisely where the demand side (shown in red at the top of Figure 3) is unable to proceed satisfactorily in the activities below (shown in green in Figure 3). The Ministry of Health, Welfare and Sport's justification for drawing up an agenda for medical product research incentives is that this safeguards the interests of care within the innovation system.

2.6 Conclusion: the justification criteria

The above analysis identifies the three criteria that are most usable in determining whether the Ministry of Health, Welfare and Sport's involvement in funding and steering the research and development of specific medical products is truly legitimate. In other words, within this framework, when can we say that public money has been well spent?

1 Present public interest: care that is in need of improvement and/or opportunities to achieve health gains.
   The public duty to ensure good and efficient care justifies government incentives for research into medical products, and for the innovation of such products. Furthermore, because it sets policy priorities, the government is sometimes the 'problem owner'. Take, for example, the issue surrounding labour productivity in the care sector. This priority setting means that innovations that promote labour productivity must be marketed, and in that sense the government is part of the pull.
2 Market failure.
   There is a supply and demand mismatch because key processes in the innovation system perform poorly. The government shares responsibility with the other players in the innovation system for improving this situation.
3 A satisfactory knowledge base in the Netherlands.
   Effective innovation, but more particularly efficient innovation, requires an adequate knowledge base in the academic world and in industry. This needs to be coupled with development and marketing know-how concerning the products in question.

These three criteria, which justify the broad sweep of government incentives for medical products research, are reflected in the centre panel of the triptych: the 'what' question. The Committee has used refined versions of these criteria to create a firm research agenda.

Chapter 3

The research agenda (the ‘what’ question)

3.1 Introduction

The Committee argued in Chapter 2 that the funding and shaping of health research by the government is justifiable. Research agendas are tools for ensuring that control and funding are carried out efficiently and effectively. It was with this in mind that the Minister of Health, Welfare and Sport asked the RGO to draw up a medical products research agenda. In order to carry out this assignment, the Committee was compelled to make various choices. The most important is the prominence given to the user perspective (pull). This prominence will help ensure that the research agenda includes desirable medical products rather than, as the Minister requested, areas of research to be promoted. Furthermore, given the time constraints involved, the Committee was obliged to restrict itself to a limited number of disease areas. Fifteen areas were finally selected. The considerations underlying these choices are explained in Section 3.2.

The method for drawing up the research agenda is set out in Section 3.2, with details in Annex G. This method ultimately led to a list of medical products that users had put in their top three. Section 3.2.3 addresses the criteria used by the Committee to determine which of the medical products are eligible for inclusion in the research agenda. The results are presented in Section 3.3, after which the related clustering is addressed in Section 3.4. The Minister specifically requested

the RGO to take account of several previous reports; Annex H briefly summarises the relationship between the research agenda and the previous reports. Where appropriate, details are given of the comments made by the experts interviewed. In Section 3.5 the Committee sets out its conclusions, which contributed to the recommendations given in Chapter 5.

3.2 Method

This section outlines the method used in determining the content of the research agenda. Details of the method are given in Annex G.

3.2.1 Justification of choices made

The Committee was obliged to make choices in order to render the Minister's request manageable, given the time and resources available. Three choices and the attendant limitations call for discussion here: focus on the needs; medical products versus areas of research; and the selection of fifteen disease areas.

Focus on the needs

The Minister explicitly requested that the agenda be drawn up from a public perspective. The Committee therefore opted to focus on user needs – i.e. those of patients and care providers (pull). This approach helps to clarify user demand and to expose any mismatch between supply and demand (market failure). It is also consistent with one of the three themes within the mission of the Care Innovation Platform: 'A people focus: improving the position of patients and professionals'.[22]

However, this approach also has potential limitations. For instance, some questions, such as about the desirability of certain developments from an ethical standpoint, were neither asked nor answered. Neither did the Committee incorporate this aspect in its criteria (see Section 3.2.3).

Furthermore, with this approach other perspectives may be overlooked, resulting in gaps in the research agenda. The World Health Organisation (WHO) for instance uses the global burden of disease as a starting point for its *Priority Medicines*: *Managing the Mismatch* and *Priority Medical for Europe and the World* reports, which also address the needs of non-Western countries.[21,23] Whether or not this has actually resulted in substantive gaps is something that can only be ascertained with hindsight. This issue is discussed in more detail in Section 3.4.3.

Medical products versus areas of research

The Minister asked the Committee to identify those areas of research with the best prospects of successful applications, however, it opted for a different perspective. Instead of areas of research that might lead to desirable medical products, the Committee focused on the desirable medical products themselves. The Committee had three reasons for adopting this approach.

The first was that opting for the user perspective (pull) as the starting point makes the medical products perspective almost inevitable, because pull parties think in terms of specific medical products rather than the associated areas of research. The Committee decided against trying to trace medical products back to the required areas of research, given the complexities involved.

The second reason was that the government frequently acts as a push party, while its role as a public party means that the government might sometimes be better advised to act as a pull party. Push parties – the academic world and industry – know their strengths and actively pursue them, potentially influenced by public demand from the pull. The government adopts a double role in this arena. On the one hand the government is a knowledge user, and the development of knowledge and products is important for its policy domains (pull). On the other hand it seeks to provide a stimulus to the knowledge economy. This can involve identifying promising candidates for innovation and giving them additional incentives (push). This report involves a medical products research agenda in which public needs (demand) and market failure (imbalance between supply and demand) play pivotal roles. Accordingly, the Committee felt that the government should ideally act in this case as a pull party, and opted for the perspective of specific products as opposed to areas of research.

Finally, if the research agenda were to be approached from the perspective of providing a stimulus to areas of research, there is a risk that key processes in the innovation system (other than knowledge development) might not receive the attention they deserve. This could lead to the desired innovations failing to materialise, despite the investment in knowledge development. By opting for the medical products perspective the Committee aims to encompass the entire innovation cycle.

Opting for medical products rather than areas of research has made the research agenda far more tangible. A possible risk is that the agenda would project insufficient long-term vision. In order to limit this risk the Committee increased the level of abstraction by arranging specific medical products in clusters. The clusters are expected to safeguard the long-term vision, the very specific

products they contain serve to illustrate users' needs. The Committee views the latter point as a major advantage.

Choice of fifteen disease areas

In consultation with the Athena Institute, the opinions of patients and care providers (pull) were obtained in focus groups (see also the background study[1]). The patients in a focus group ideally share some communal basis (a certain degree of homogeneity). At the same time, qualitative research demands a large degree of variation. The Committee therefore opted to use disease areas as a starting point (the communal basis) and to select focus group participants so as to represent as many different disorders within the respective disease areas as possible. Because time and resources were limited in the advisory project, the Committee was obliged to limit the number of disease areas it addressed. Details of the selection process are given in Annex G. Table 2 shows the fifteen disease areas included in this research agenda. The abbreviations for the respective disease areas used in the rest of the document are shown in brackets.

Table 2 The fifteen disease areas about which patients were consulted. The abbreviations, which refer to the respective disease areas, are shown in brackets and are used throughout the report.

Disease areas without an existing research agenda:	
1	Locomotor disorders (loco.)
2	Anxiety disorders (anx.)
3	Cardiovascular disorders (heart)
4	Cerebrovascular accident (CVA)
5	Dementia (dem.)
6	Depression (depr.)
7	Gastrointestinal and liver disorders (GLD)
8	Visual impairment (vision)
9	Orphan diseases (orphan)
Disease areas with a research agenda:	
10	Respiratory disorders (resp.)
11	Burns (burns)
12	Diabetes (DM)
13	Kidney disorders (kidney)
14	Muscle disorders (muscle)
15	Intellectual disability (intel.)

Care providers were also consulted in focus groups. Because their opinions were sought about disease-transcending topics, the selection was on homogeneity in terms of profession. Focus groups were arranged for general practitioners, nurses

and medical specialists. Informal carers were consulted for several disease areas, as patient supervisors.

3.2.2 *Consultations*

As stated, the Committee opted to take as its starting point the perspective and needs of medical product users (pull; patients, physicians, nurses, and informal carers). The opinions of the push side (science and industry) were solicited about trends in groundbreaking research, predictions for the coming five to ten years, and obstacles in the innovation system that would form a barrier for the foreseen innovations. Finally, Ministry of Health, Welfare and Sport policymakers helped to create a picture of the policy context and needs that they perceive from the perspective of policy.

The involvement of patients – an important subgroup of the pull-side – in drawing up research agendas is not new. Health funds and the Netherlands Organisation for Health Research and Development (ZonMw) in collaboration with patients' organisations have previously drawn up research agendas for several disease areas, such as asthma and chronic obstructive pulmonary disease (COPD).[24] The Committee used these results in their deliberations. Furthermore, it is an RGO tradition that patients and their representatives participate in drawing up recommendations for scientific research and infrastructure. In 2007, the RGO recommended the further development of user involvement, including through research.[25]

Nonetheless, the approach chosen in this document is new to the Netherlands. Never before has the user perspective formed the starting point for a centrally formulated disease-transcending research agenda. The United States Institute of Medicine (IOM) recently performed a similar exercise on comparative effectiveness research.[26,27] The IOM report describes how priorities were assigned to research of this kind in the context of President Obama's economic stimulus programme. In brief, experts and the parties involved worked in a process of intensive and large-scale consultation on prioritising research with special relevance to health and care. The approach included an Internet survey. The Committee studied this consultation process and several other examples, before assessing their applicability to the Dutch situation.

A diagram of the method selected for arriving at a medical products research agenda is shown in Figure 4. The method is partly experimental in nature. The emphasis is on a relatively unexplored area: systematically mapping out the

wishes and requirements of patients and care providers in the direct care sector – the pull side (see the red blocks in Figure 4). Which medical products do they need?

A potential limitation of this approach is that users may start to 'daydream'. It is therefore important to balance the demand to satisfy users' needs with what researchers and industry – the push – view as realistic in the next five to ten years. This is why the opinions of scientific and industrial experts were solicited and incorporated before, during (in a focus group), and after sounding out users' needs (see the green blocks in Figure 4).

The Committee finally weighed and prioritised the suggested products based on the members' own competence and expertise (shown in grey in Figure 4). Patterns identified in the suggested products facilitated a form of clustering.

As stated above, the working method outlined here is partly experimental in nature. A consequence of is that the experience gained and the lessons learned for the future are significant components of this document.

3.2.3 Criteria

The Minister observes in his request for advice that public funding of R&D by the Ministry of Health, Welfare and Sport requires clear justification, and he asked the RGO to recommend selection criteria for potential research candidates. The Committee discussed the justification above in Chapter 2: Section 2.5 presents three criteria. The Committee has operationalised the first criterion (added value for the care sector) in greater detail, producing the following set of six criteria.

Added value for the care sector

1 What health gains are there for individual patients (lower mortality and morbidity, higher quality of life)?
2 How large is the patient group for which the product may have added value in the Netherlands?
3 What savings or additional costs per patient would the product entail relative to the current situation?
4 What impact would this product have on the need for professional care, relative to the current situation?

Market failure

5 Are there any clearly identifiable reasons why industry will not undertake development of the product?

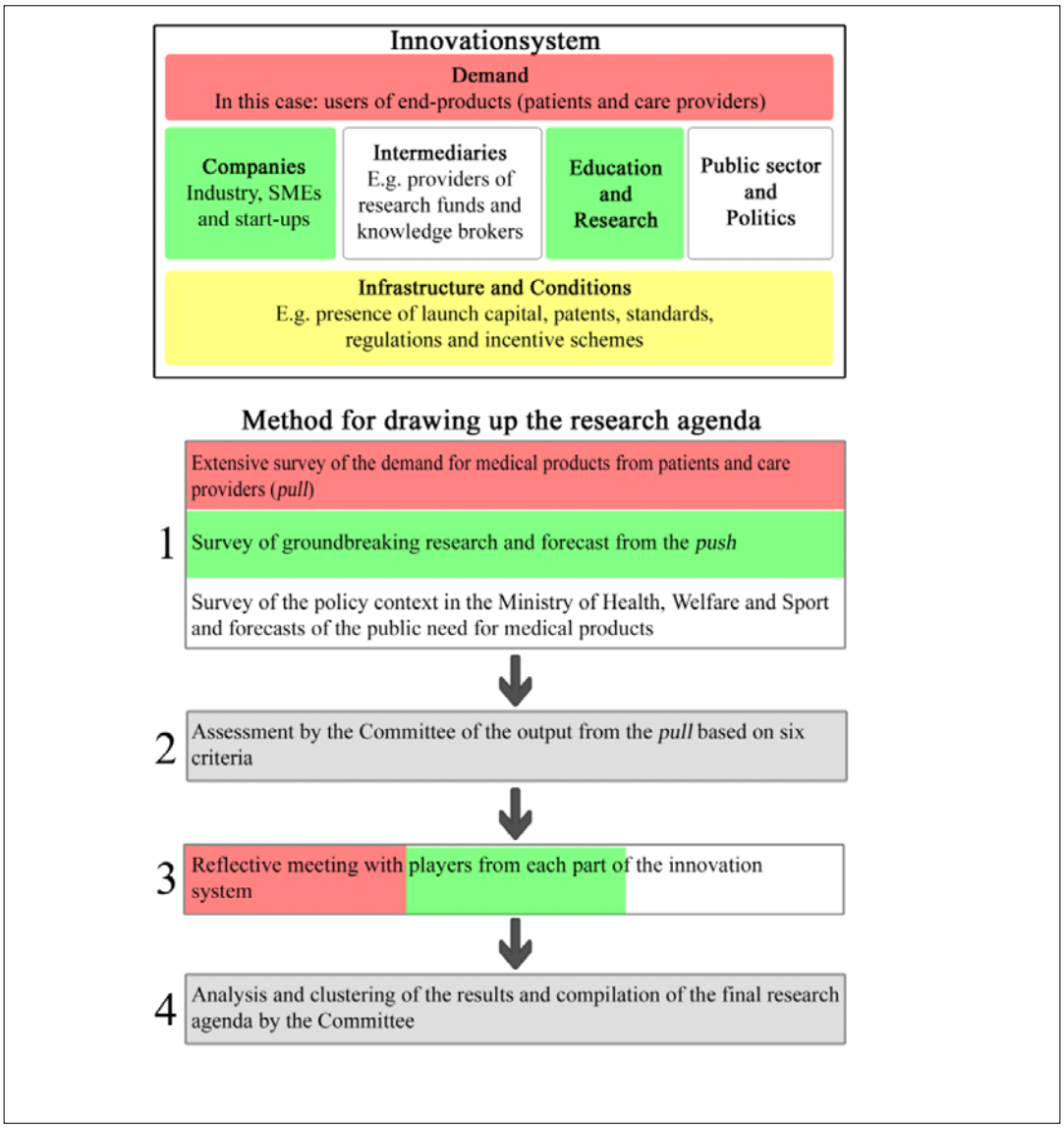

Figure 4 Diagram of the method of generating the research agenda. The constituents of the innovation system are again at the top, below which are the steps taken to arrive at the present research agenda (Section 3.4). The colours show the parties involved in the step concerned: red: pull (patients and care providers); green: push (academia and industry); white: other players in the innovation system (government and/or intermediaries); grey: the Committee alone.

Knowledge base

6 Is the knowledge base adequate for successful development of the product in the Netherlands (research infrastructure, technical expertise and development and marketing know-how)?

The first three criteria are actually ingredients of the traditional cost-effectiveness assessment, and as such will also be usable in the future as operationalisation of the added value for the care sector criterion. The fourth criterion will be relevant in the coming decades, as population ageing results in more people needing care that fewer people are available to provide.

The Committee used criteria 1 to 5 in appraising the medical products suggested by the patients themselves. Criterion 6 state is unconnected with the value of the product and was used mainly in assessing whether the initiative for developing the product concerned should come from the Netherlands.

Not all criteria carry equal weight in prioritising the medical products. The Committee followed the AHP method (see Annex G) to determine the weight of each of the criteria in the final assessment of the medical products. The result is shown in Table 3.

3.2.4 Reflection meeting

The Committee considered it important to bring the pull and push parties together for discussion at the end of the process. The reflection meeting that was arranged for this purpose provided an opportunity to reflect on both the process (1) and the outcome (2): 1) what were the opinions about the chosen methodology: were the right people interviewed and the right questions asked, and what lessons have been learned about the method; 2) what are the reactions to the outcome: did the Committee handle all the contributions from pull and push satisfactorily; are there any points for improvement, and were any points underilluminated? The session also provided the participants with an opportunity to consider the question of how the research agenda should be implemented: should a programme be set up; if so, who should be involved; should the programme be highly specific, or on a somewhat higher level of abstraction? Details of the reflection meeting are given in Annex E and Annex G.

Table 3 Criteria weights, determined using the AHP method (see Annex G). The total of the weights is 1. If all criteria were to have the same weight, they would score 0.2.

1	Health gain	0.39
2	Target group size	0.12
3	Costs per patient	0.17
4	Labour saved	0.10
5	Market failure	0.22
6	Knowledge base	N/A

3.2.5 *Lessons learned from the method*

The method used is experimental in nature and therefore yields lessons for the future.

The patients were surveyed in focus groups, which is an appropriate method of gathering qualitative data. An attendant risk is that a certain bias may occur, e.g. through the choice of individuals in the focus groups. An attempt was made to eliminate any bias of this kind by involving experts who were familiar with a disease area. An additional way of acquiring more quantitative data is to survey large groups – e.g. by means of an Internet survey – based on focus group output. It would be worthwhile considering this option in future.

Focus groups were also used to solicit the opinions of care providers. Four types of care providers were chosen. However, this generated too few homogeneous groups, as the thinking of the focus group participants was primarily based on their own disease-related background. The general practitioners were an exception in this regard as, to a lesser extent, were the nurses. The output of these focus groups was therefore less specific than had been hoped, and there was a sense of arbitrariness about the specific medical products that did emerge. In order to clearly identify the specific needs of the care providers, future surveys should be more extensive, and should involve groups that are more homogeneous in terms of specialisation.

Prioritising individual medical products based on these criteria works well, provided that these are specific products for a clear target group. Disease-transcending assessment – which the Committee attempted for the ‘personalised medicine’ category – does not work well. The various assessors were far from unanimous about the goals to be achieved by personalised medicine, which was detrimental to the reliability of the appraisal. Future assessments of this kind should always be performed in clusters for individual specific medical products.

These lessons for the future notwithstanding, the Committee considers that the method developed has withstood the experimental phase well. The ultimate validation will have to come when the results delivered by the research agenda are evaluated. One important question is: did the research agenda give rise to medical products that satisfy the needs of patients and care providers? Another is: would it have been much more difficult or even impossible to market these products without the present research agenda?

3.3 Presentation of the results

3.3.1 Total input of the pull (patients and care providers)

Table 4 shows the medical products identified by patients in the fifteen disease areas as “major needs”. The products in the respective disease area considered most important by the patients are shown in italics (‘top 3’). Table 5 is a summary of the input from care providers regarding the need for medical products. The method used in generating these tables is set out extensively in the Athena Institute background study, which is attached to this document.[1]

Tables 4 and 5 illustrate what users are keen to see included in the research agenda. It should be noted that the survey used has some limitations. The contribution of patients was limited to fifteen disease areas and the sample of professionals was rather small. Nonetheless, numerous noteworthy findings emerged.

Table 4 The output from patients, across fifteen disease areas. The three medical products considered most important by the patients are shown in italics. The numbering in the first column does not indicate ranking.

Locomotor disorders (loco.)	
1	*Determine in advance the most effective medication based on individual (disease) characteristics*
2	*Cartilage and bone regeneration*
3	*Gait analysis devices*
4	Anti-fatigue agent
5	Early and correct diagnosis of osteoarthritis, e.g. using biomarkers
6	Effective pain control
7	Tailored devices for daily life
8	Improved anti-inflammatory agents (more effective, fewer side effects)
Respiratory disorders (resp.)	
9	*Individualised medication (including on the basis of age)*
10	*Method for early and correct diagnosis*
11	*Product for reducing or eliminating fatigue*
12	Tissue regeneration of the lung
13	Anti-inflammatory agents without the unpleasant side effects of Prednisone
14	NO meter (to measure inflammatory response in lungs) for home use

15	Improved medication delivery methods to replace inhalers, aerosols and drips
16	Improved lung transplants using a non-heart beating technique and prior lung enhancement
Anxiety disorders (anx.)	
17	*Individualised medication (based on genetics and blood values of medicine)*
18	*Products for biofeedback*
19	*Products to counter fluctuations in sex hormone levels*
20	Medication without starting and tapering issues
21	Improved medication (more effective, fewer side effects)
22	Neuromodulation techniques (e.g. deep brain stimulation), preferably non-invasive
23	Imaging technology for faster and more accurate diagnosis
Burns (burns)	
24	*Effective anti-itching agent for scars*
25	*Tissue regeneration of the skin*
26	*Better prevention and treatment of wound infections and inflammation*
27	Medical products for scar firming
28	Better dressings that cause less pain when being changed and that stay less moist because of oedema formation
29	Ergotherapeutic devices, e.g. tailored cutlery
30	Pigment applicator for affected skin
31	Improved pressurised garments, pressure masks and silicone gel plasters (more effective, user-friendly and comfortable)
32	Medical products to counter neuropsychological symptoms such as concentration disorders, fatigue, sleep problems and memory disorders
Cardiovascular disorders (heart)	
33	*Myocardial stem cell therapy*
34	*Individualised medication*
35	*Reduction of statin side effects*
36	Stents for medication delivery
37	Cardiostick containing the patient file
Cerebrovascular accident (CVA)	
38	*Improved alternative for immediate postinfarct thrombolysis*
39	*Products for home convalescence*
40	*Neuralgia treatments*
41	Medication based on individual characteristics
42	Improved orthopaedic footwear, and fitting
43	Home diagnosis for blood pressure and cholesterol
Dementia (dem.)	
44	*Product for stabilising dementia (dementia inhibitors)*
45	*Targets for medicinal remedies from food*
46	*Devices to minimise the unfavourable consequences of memory impairment*
47	Devices for reducing loneliness (modern forms of telecommunication, comfort cushion)
48	Home automation (domotics) for remote assistance (GPS, sensors and monitoring systems)
Depression (depr.)	
49	*Better antidepressants (faster acting, more effective, fewer side effects)*
50	*System for measuring biomarkers (yet to be identified) in blood, firstly for diagnostics, and secondly for personalised medicine*
51	*Neurobiological technology for specific brain areas (comparable with TMS, NVS and DBS)*

52	Genetic test for risk detection, diagnosis and classification of the depression
Diabetes (DM)	
53	*Agent for increasing the sensitivity of body tissues to insulin (type II)*
54	*Combined sensor and pump for blood glucose regulation*
55	*Diagnostic tests (biomarkers) for detecting complications*
56	Tissue regeneration for the Islets of Langerhans (type I)
57	Meter to give timely warning of low blood glucose and impending hypoglycaemia
58	Non-invasive insulin delivery method
59	Medication for diabetic neuropathy
Gastrointestinal and liver disorders (GLD)	
60	*Active ingredients in food that have an influence on the disorder and medication, as a remedy*
61	*Less invasive diagnostic methods to replace endoscopy (expressly including gastroscopy)*
62	*Biomarkers to improve medication*
63	Hormonal targets (involving both sex and stress hormones) for medication
64	Improved medication delivery methods for Crohn's disease and colitis ulcerosa to replace large tablets, enemas, drip-feed and the administration of biologicals
65	Home diagnosis for inflammation values in blood and stools
66	Pain medication
67	Improved constipation medication (fewer side effects)
68	Improved stomas with greatly reduced risk of internal and external complications
69	Improved stomas for children
70	Anti-fatigue agent for liver disorders
Kidney disorders (kidney)	
71	*Implantable biological artificial kidney*
72	*Forms of dialysis with fewer complications and limitations*
73	*Reduction of side effects of anti-rejection medication*
74	Home meter for blood values related to renal function
75	Reduction of side effects of medication for kidney disorders
76	Early and correct diagnosis, in particular for people with rare or hereditary kidney disorders
77	Mobile and compact home dialysis device
Muscle disorders (muscle)	
78	*Effective pain control*
79	*Brain-Computer Interfaces*
80	*Genetic repair (e.g. exon skipping)*
81	Early, correct and less invasive diagnostics
82	Improved respiratory support and PEG tube
Intellectual disabilities (intel.)	
83	*Improved neonatal screening*
84	*Improved communication devices*
85	*Individualised medication*
86	Home automation (domotics), such as camera systems, sensor systems for getting out of bed, fingerprint-operated entrance doors
87	Brain stimulation to improve cognitive skills

Visual impairment (vision)	
88	*Reading systems for 'everyday products'*
89	*Improved navigation systems*
90	Early and correct diagnosis
91	More ergonomic devices (including white stick and guide harness), leaving both hands free
92	Improved software for Internet use
93	Optic nerve regeneration
94	Improved medication delivery methods, e.g. eye injections and eye drops
95	Tailored filter spectacles (both functionality and aesthetics)
96	Medical products to counter fatigue caused by compensating for the lack of visual stimulus
Rare disorders (orphan)	
97	*Gene therapy*
98	*Medication for reducing or eliminating symptoms in the short term*
99	*Centres of expertise*[a]
100	Medication for ossification in FOP
101	Expansion of neonatal screening
102	Expansion of pre-implantation genetic diagnostics

[a] Since centres of expertise are not medical products, there was no further assessment of this patient need.

Table 5 The output from four groups of care providers. The numbering in the first column does not indicate ranking.

General practitioners	
103	Improved medication delivery methods for polypharmaceutics
104	Devices to counter pain and incontinence (nonmedicinal)
105	Improved information systems for both general practitioner-to-general practitioner and general practitioner-to-patient
106	Rapid and simple diagnostic medical products for primary care (mobile X-ray, ultrasound scan with image recognition)
Informal carers	
107	Devices to enhance independence (communication devices, software, user-friendly devices)
108	Home automation (domotics) for remote assistance (GPS, sensors, software)
Medical specialists	
109	Improved imaging technology (greater contrast and reduced radiation)
110	Diagnostic tests based on metabolic changes
111	Improved medication, so that fewer pills are needed
112	Improved stents for poorly accessible places
113	Biomarkers to improve diagnosis and therapy
114	Gene therapy and stem cell therapy
115	Devices to promote behavioural change to prevent major disorders such as diabetes and cardiovascular disorders
116	Medical products for early risk diagnosis of major diseases such as diabetes and cardiovascular disorders
117	Device for measuring and supporting patient compliance
Nurses	
118	Improved information systems (bedside mobile recording system, data accessible anywhere, complete patient file in a single system)
119	IT systems for storage and distribution of EBP protocols
120	E-learning modules
121	Devices for remote care (e.g. webcam)
122	Devices for interactive patient information provision

It is clear firstly that patients and care providers approached their needs for medical products from their own perspective, and that these perspectives are complementary. For instance, patients' contributions were spread equally across the three types of products (pharmaceuticals, devices for diagnosis and care, and tissue-replacement products), while the care providers were predominantly concerned with devices for diagnosis and care. The latter group, albeit as the Committee wished, was more focused on the conduct of the profession, and therefore tended to emphasise devices with the potential to assist in care provision. In this light, it comes as no surprise to find that care providers leaned largely towards organisational processes, such as information storage and sharing. Ultimately, patients too consider organisation of the care sector to be an important subject (see background study by the Athena Institute). However, because the focus was on medical products to improve care, only a few of them identified specific products to alleviate the organisational obstacles they observed in the care sector.

The second point to note is that patients arrived at a good mix of short and long-term perspectives. Some doubts about the Committee's methods were originally expressed from professionals in this field, because it was felt that patients would favour the short-term solutions, and ignore the long-term perspective. With hindsight, these concerns would appear to have been unfounded. Patients seem to be well informed about scientific progress in general, and about the trends in areas such as regenerative medicine and personalised medicine.

Thirdly, the Committee observes that, from the perspective of the pull, setting a research agenda gives rise to gaps, most conspicuously in prevention. Patients' apparent lack of regard for public health, as well as for primary and secondary prevention, might have been an artefact of the phrasing of the Committee's questions. In contrast, they did have a strong interest in tertiary prevention in the form of diagnostics for monitoring disease, in the early detection of complications, and in lifestyle interventions. Similarly, prevention in general was not a major consideration for the care providers in the focus groups. Some themes that did not come from the pull, but were raised by the government, or the push, are presented in Section 3.4.3.

Finally, it was noted that patients mentioned as many products designed to help them live with their disorder as products designed to treat the disorder itself. While patients obviously want effective diagnosis and therapy for their particular disorder, they equally often want products that deal with the consequences of the disorder or the treatment. This includes tackling symptoms with a (sometimes serious) effect on quality of life, such as fatigue, pruritis and pain, reduction of

the side-effects of pharmaceuticals, and less invasive medication delivery methods. Medical products targeting these kinds of needs have a broader scope than the disease area about which the needs were initially expressed.

3.3.2 *Prioritisation*

In the prioritisation of the medical products the Committee focused on the 'top 3' mentioned for each of the fifteen disease areas. The medical products were required to be specific enough to allow assessment in accordance with criteria discussed in section 3.2.3, which was not the case for all the top 3 products. In the end, 28 specific products were assessed. Patients put the product personalised medicine in the top 3 for multiple disease areas, and, despite not being very specific, it was adopted as a disease-transcending product. The products that the Committee prioritised are shown in Table 6. The corresponding numbering will be used below in this report. The output of the prioritisation exercise is given in Figure 5, in order of priority.

There are several noteworthy points. The variability with respect to the 'health gain' criterion remained modest. It must be borne in mind that patients had put all the products under consideration in the top 3. Generally, the Committee evidently concurred with the prioritisation given by the patients. Conversely, the variability between the products on the 'market failure' criterion was relatively large. This has a pronounced effect on the scores, because market failure was given the highest weighting factor after health gain.

3.3.3 *Assessment of the knowledge base*

The sixth criterion – a good knowledge base – was assessed separately because it is unrelated to the value of the product. The findings, which are shown in Figure 6, shed light on the opportunities in the Netherlands for successfully developing the product concerned. This is because the chances of success are determined by the quality of the knowledge base.

There was considerable variability between products in terms of their score on the 'knowledge base' criterion. For some products there was a definite need for development, but the Committee judged that the market would not develop the product unaided. For some of these products moreover there is insufficient expertise and infrastructure in the Netherlands to tackle the development with public funds. The Committee appeared to be reasonably consistent in this assessment.

Table 6 The medical products weighed by the Committee based on the criteria. The numbering will be used below in this document.

1	Gait analysis device (loco.)
2	Cartilage and bone regeneration (loco.)
3	Product for reducing or eliminating fatigue (resp.)
4	Biofeedback (anx.)
5	Products to counter fluctuations in sex hormone levels (anx.)
6	Anti-itching agent for scars (burns)
7	Skin regeneration (burns)
8	Reduction of statin side effects (heart)
9	Myocardial stem cell therapy (heart)
10	Neuralgia treatment (CVA)
11	Alternative for immediate postinfarct thrombolysis (CVA)
12	Devices to counter memory impairment (dem.)
13	Dementia inhibitors (dem.)
14	Better antidepressants (depr.)
15	Diagnosis based on biomarkers (depr.)
16	Combined sensor and pump (DM)
17	Increase insulin sensitivity (type II; DM)
18	Alternative for endoscopy (GLD)
19	Active ingredients in food (GLD)
20	Implantable biological artificial kidney (kidney)
21	Less harmful forms of dialysis (kidney)
22	Pain control (muscle)
23	Brain-computer interfaces (muscle)
24	Communication devices (intel.)
25	Neonatal screening (intel.)
26	Navigation systems (vision)
27	Early and correct diagnosis (vision)
28	Gene therapy (orphan)
29	Personalised medicine (disease-transcending)

Comparing Figure 5 and Figure 6 reveals a striking disparity. There is no satisfactory Dutch knowledge base for some high priority products, nor does the existence of a satisfactory knowledge base necessarily imply a great need for the kind of products involved. However, the lack of a satisfactory knowledge base does not lead inevitably to the conclusion that the Dutch government should not invest. If, no other countries possess the necessary knowledge base, for example, this might actually represent an opportunity for the Netherlands. This topic will be considered in more detail in Section 3.4.

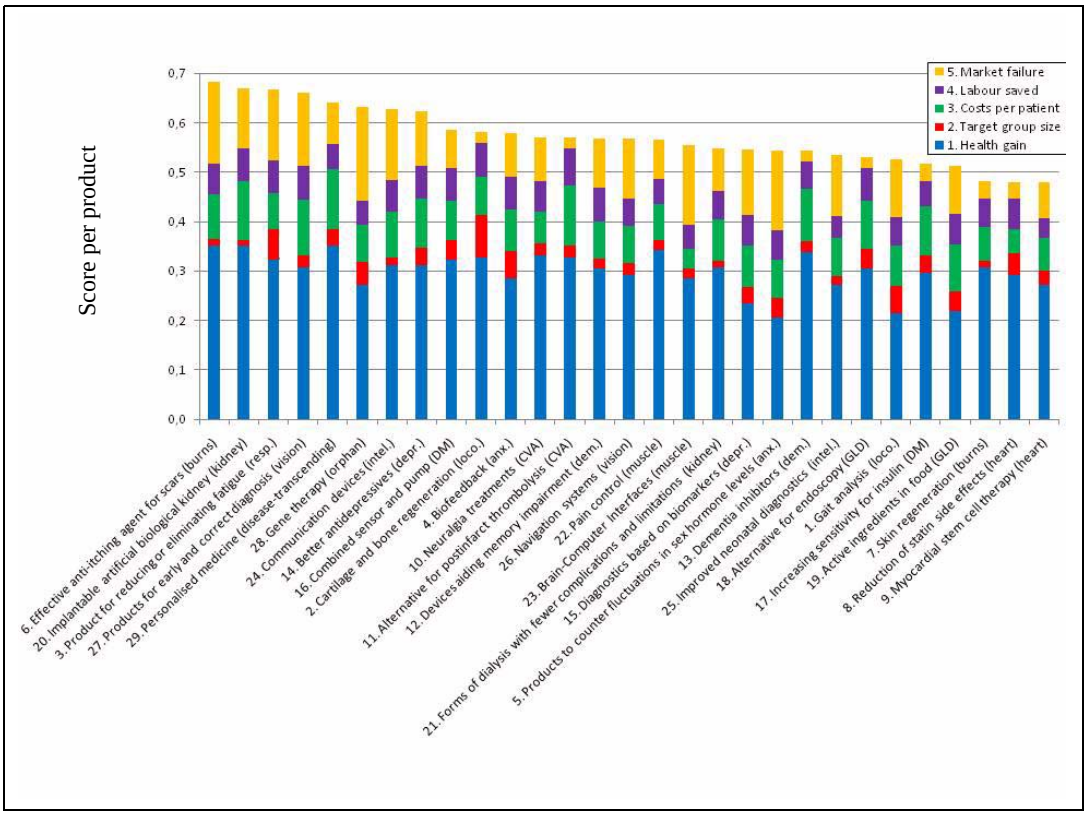

Figure 5 Prioritisation of the medical products mentioned by patients based on five criteria (i.e. without the 'knowledge base' criterion). The y-axis shows the score per criterion, totalling a maximum of 1. The x-axis shows the individual medical products, with the disease area shown in brackets. See Table 1 for the abbreviations used. Personalised medicine (or variants) was mentioned in multiple focus groups, and was therefore classed as disease-transcending.

3.4 Clustering of the output: the research agenda

While considering the output of the surveys the Committee concluded that it should not restrict itself to putting the top 3 products on the agenda, but should do justice to the entire body of information. It is striking that many of the products were mentioned in multiple disease areas. This fact led the Committee to define disease-transcending product clusters, immediately eliminating any limitation imposed by the disease areas that were used. By identifying clusters, the Committee also wished to establish a long-term vision.

This section shows how the results were clustered into a research agenda and identifies those for whom it is relevant.

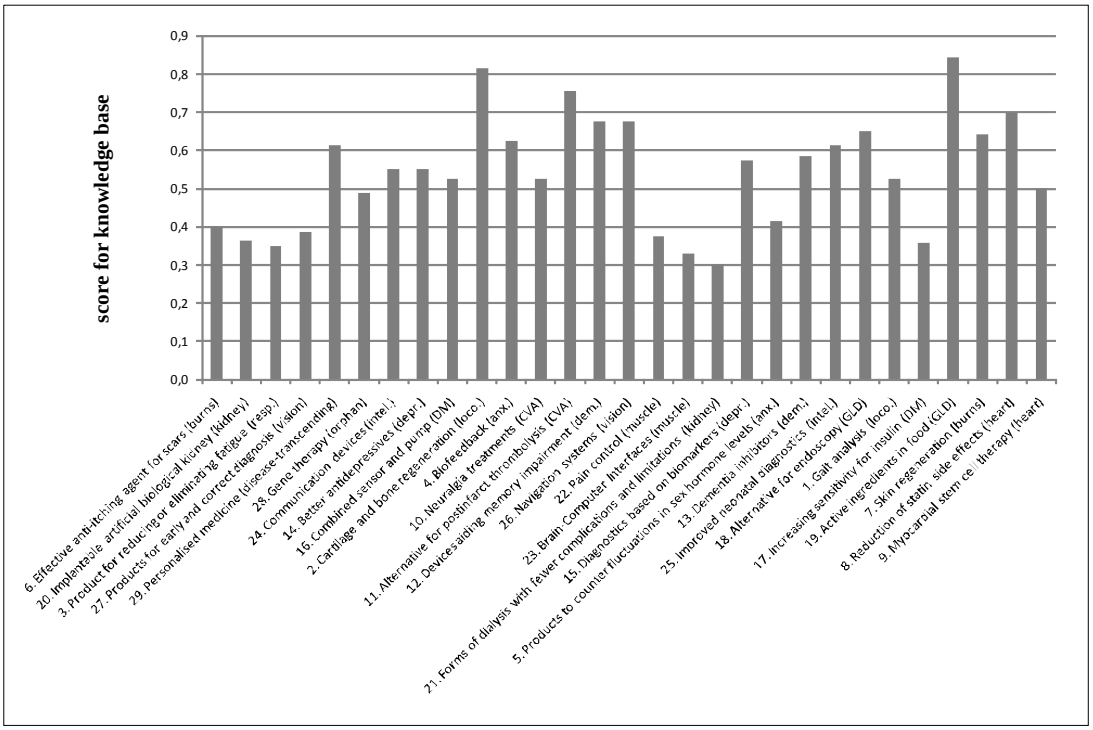

Figure 6 Score for the medical products mentioned by patients based on the 'knowledge base' criterion. The y-axis shows the score for 'good knowledge base', with a maximum of 1. The x-axis shows the individual medical products, with the disease area shown in brackets. See Table 1 for the abbreviations used. Personalised medicine (or variants) was mentioned in multiple focus groups and was therefore classed as disease-transcending.

3.4.1 Clustering

The clustering involved identifying those products that belong together in a technical sense. Products can be clustered on the basis of various criteria, such as the purpose of the product (e.g. self-management, personalised care, diagnosis, and so on), or the effect of the product (e.g. oriented to the disorder itself, or to how to live with the disorder). All these aspects were considered in arriving at the final clustering.

Products that fall into the same category on the basis of several different criteria can be said to have a strong relationship. The objective was to identify clusters of some considerable size, thereby ensuring that the clusters do not

degenerate into catchalls. This analysis produced eight clusters from the patient's perspective and two from the care provider's perspective (Table 7).
Table 7 shows the 44 medical products from the top 3 of each disease area in Clusters A to H. The medical products mentioned by care providers that do not fall into Clusters A to H are shown in Clusters I and J. It goes without saying that the application opportunities of the clusters extend beyond the products mentioned here; medical product development for other disease areas may also be relevant in each of the clusters.

Table 7 Ten clusters of medical products, eight of which from the perspective of the patient (A to H) and two from the perspective of the care provider (I and J). Clusters A to H have the top 3 medical products of each disease area. For the abbreviations see Table 2, and for the numbering see Table 6. The unnumbered medical products were not weighed using the criteria. Clusters I and J contain the needs of care providers that do not fit within the eight clusters created from the patient's perspective.

A	Regenerative medicine (tissue regeneration and gene therapy)	
	2.	Cartilage and bone regeneration (loco.)
	7.	Skin regeneration (burns)
	9.	Myocardial stem cell therapy (heart)
	20.	Implantable biological artificial kidney (kidney)
	-	Genetic repair (e.g. exon skipping[a]) (muscle)
	28.	Gene therapy (orphan)
B	Personalised medicine	
	29.	Advance determination of the most effective medication based on individual (disease) characteristics (loco.)
	29.	Individualised medication (including on the basis of age) (resp.)
	29.	Individualised medication (based on genetics and blood values of medicine) (anx.)
	29.	Individualised medication (heart)
	29.	Biomarkers to improve medication (GLD)
	29.	Individualised medication (intel.)
C	New medical products targeting the effects of the disorder (quality of life)	
	3.	Product for reducing or eliminating fatigue (resp.)
	6.	Effective anti-itching medical product for scars (burns)
	10.	Neuralgia treatment (CVA)
	22.	Effective pain control (muscle)
D	Improved versions of existing medication	
	8.	Reduction of statin side effects (heart)
	14.	Better antidepressants (faster acting, more effective, fewer side effects) (depr.)
	-	Reducing the side effects of anti-rejection medication in organ transplants (kidney)
E	New medical products targeting the disorder	
	5.	Medical product to counter fluctuations in sex hormone levels (anx.)
	-	Better prevention and treatment of wound infections and inflammation (burns)
	13.	Product for stabilising dementia (dementia inhibitors) (dem.)
	-	Targets for pharmaceuticals from food (dem.)
	17.	Agent for increasing the sensitivity of body tissues to insulin (type II) (DM)
	19.	Active ingredients in food that have an influence on the disorder and medication, as a remedy (GLD)

	-	Medical products able in the short term to reduce or eliminate symptoms (orphan)
F	Early, accurate diagnosis involving less discomfort	
	-	Method for early and accurate diagnosis (resp.)
	15.	System for measuring biomarkers (yet to be identified) in blood, firstly for diagnostics, and secondly for personalised medicine (depr.)
	-	Diagnostic tests (biomarkers) for detecting complications (DM)
	18	Less invasive diagnostic methods to replace endoscopy (GLD)
	25.	Improved neonatal screening (intel.)
	27.	Early and accurate diagnosis (vision)
G	Patient toolkit to enhance self-management and self-reliance	
	1.	Gait analysis devices (loco.)[b]
	4.	Products for biofeedback (anx.)
	-	Products for home convalescence (CVA)
	12.	Devices to minimise the unfavourable consequences of memory impairment (dem.)
	16.	Combined sensor and pump for blood glucose regulation (DM)
	23.	Brain Computer Interfaces (muscle)
	24.	Improved communication devices (intel.)
	-	Reading systems for ‘everyday products’ (packaging in the supermarket, train ticket machine, etc.) (vision)
	26.	Improved navigation systems (vision)
H	Improvement and expansion of existing therapeutic interventions	
	11.	Improved alternative for immediate postinfarct thrombolysis (CVA)
	-	Neurobiological technology for specific brain areas (depr.)
	21.	Forms of dialysis with fewer complications and limitations (kidney)
I	Home automation systems[c] for remote assistance	
	-	Remote assistance (GPS, sensors, monitoring systems, software) (Informal carers)
	-	Home automation (domotics) (camera systems, sensor systems for getting out of bed, fingerprint-operated entrance doors) (Nurses)
	-	Devices for remote care (webcam, interactive patient information, interactive communication systems) (Nurses)
J	Information processing and information exchange systems	
	-	Improved information systems for both general practitioner-to-general practitioner and general practitioner-to-patient (General practitioners)
	-	Improved information flows between care providers (Specialists)
	-	Improved information systems (bedside mobile recording system, data accessible anywhere, complete patient file in a single system) (Nurses)
	-	IT systems for storage and distribution of Evidence Based Practice (EBP) protocols (Nurses)
	-	E-learning modules (Nurses)

[a] Exon skipping is a form of gene therapy in which the defective section of DNA is skipped in the translation into a protein, so that less damaged protein is produced and the disease assumes a milder form.

[b] Gait analysis would normally be categorised under diagnostics. However, because the patient perspective is paramount, it is categorised here under devices for enhancing self-management. Patients happen to want gait analysis, because it facilitates tailored advice about the exercises that will and will not benefit them, and what they should and should not do at home.

[c] Home automation systems (domotics) integrate technology and services to improve residential comfort and quality of life.

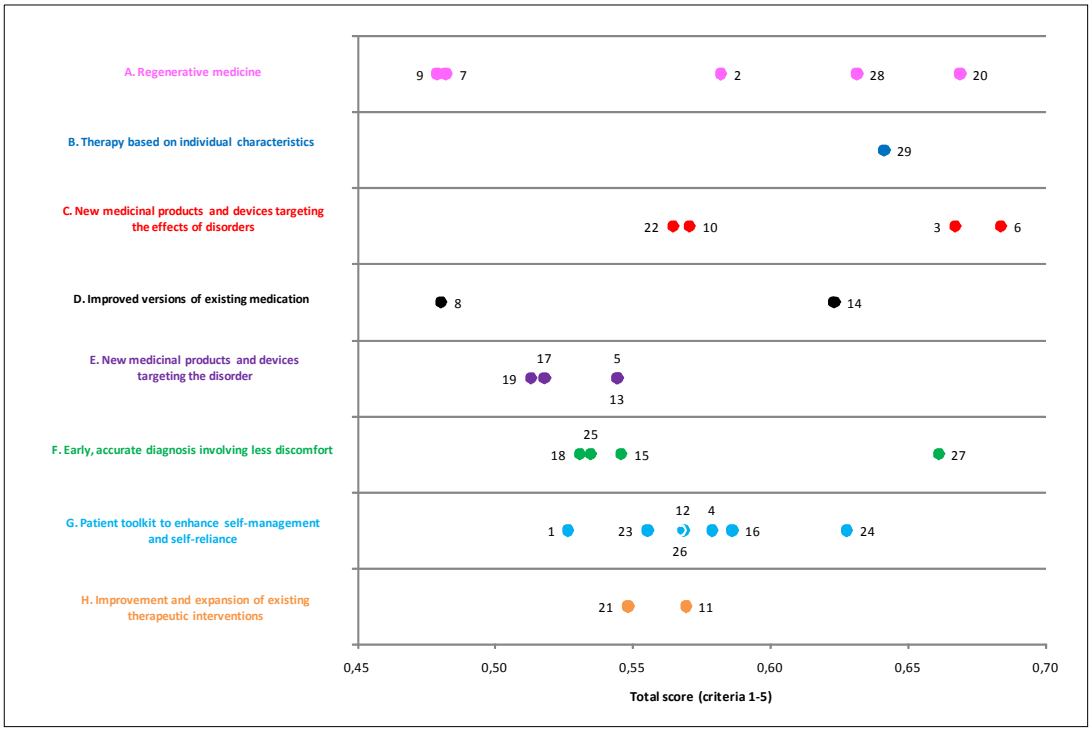

Figure 7 The spread in total score for Clusters A to H. The x-axis shows the total score on 5 criteria, the y-axis shows eight of the ten clusters (A to H). See Table 6 for the numbering. Cluster B (Personalised medicine) comprises only one medical product, because this category is classed as disease-transcending.

Based on the score for the constituent products, do some clusters deserve a higher priority than others? Figure 7 shows the scores on Criteria1 to 5 of the products per cluster. There appears to be a substantial spread, but none of the clusters is a clear exception. The same is true of the relationship between knowledge base and product (not shown).

The scores of the three groups of medical products (pharmaceuticals, devices for diagnosis and care, and tissue-replacement products) were checked to see whether one stood out from the rest. None did (not shown). Accordingly, there is no reason to give one of the three groups priority over the other two.

It can be stated that the list of medical products leads to identifiable clusters, each containing relatively low and relatively high priority products. The clustering – based on the total input from the pull – is usable as a structuring

principle of obviously relevant products. Prioritisation within the clusters would require an additional step at product level.

3.4.2 *Partners in research*

The Minister of Health, Welfare and Sport has requested an advisory report on a medical products research agenda. The Committee accordingly performed an extensive investigation into the need for products among end-users, and arranged the results in order of priority. However, this does not mean that the ensuing research agenda is a matter for the Ministry of Health, Welfare and Sport alone. Some important success factors that were mentioned above include the quality of fundamental and translational research, the development activities of industry and the innovative strength of the care sector. When things go wrong, anyone who, like the Committee, has a completely downstream view, is bound to wonder where upstream the problem occurred. This section examines the identified products and product clusters from this perspective.

Is fundamental research still the main necessity for the development of the identified products and clusters? Figure 8 provides an answer. The products are spread more or less equally across the fundamental and postfundamental phases, and most clusters have products in both phases of the innovation process.

Exceptions are Clusters C and E (‘new products targeting the effect of the disorder’ (red) and ‘new products targeting the disorder’ (purple)). All the products in these clusters require fundamental research. Most are concerned with poorly understood symptoms such as fatigue, pain and pruritis, or new therapeutic approaches related to nutrition or sex hormones. Substantial fundamental knowledge generation will be needed in order to develop products in these areas. Close collaboration with the Minister of Education, Culture and Science is appropriate.

The ‘market failure’ aspect played an important part in prioritising medical products. If the market fails to embark on the development of a product that was prioritised by the users, this is a reason for the government to introduce its own incentive schemes. What should these measures comprise? For instance, is there a relationship between market failure and the lack of a knowledge base? If so, incentives should possibly target both points, e.g. through public-private partnerships. Figure 9 shows that there is indeed a (modest) inverse relationship

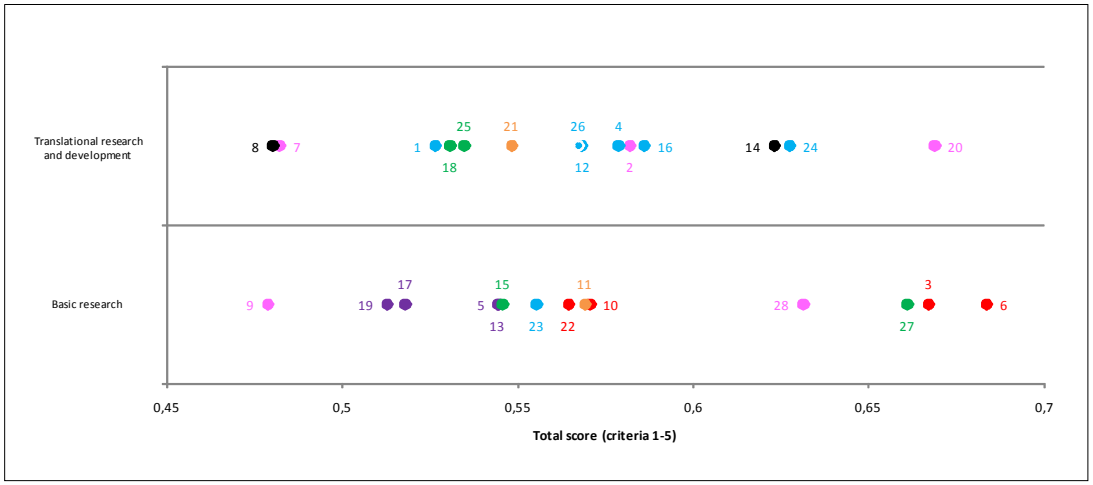

Figure 8 Medical product categories according to the need for fundamental research. See Table 6 for the numbering. Pink = Cluster A – regenerative medicine; red = Cluster C – new medical products targeting the effects of the disorder (quality of life); black = Cluster D – improved versions of existing medication; purple = Cluster E – new medical products targeting the disorder; green = Cluster F – early, accurate diagnosis involving less discomfort; blue = Cluster G – patient toolkit to enhance self-management and self-reliance; orange = Cluster H – improvement and expansion of existing therapeutic interventions. Cluster B – personalised medicine – is not shown in this figure, because it comprises only one point that is classed as disease-transcending. No products at all were assessed in Clusters I and J.

between market failure and the knowledge base: the greater the market failure, the smaller the knowledge base.*

Needless to say, the correlation of -0.5 says nothing about the cause-effect relationship. It is plausible that no powerful knowledge base would develop without interest from the market, and conversely, it is possible that a weak knowledge base would lead to little innovative market activity. The conclusion is that incentive schemes for products of this kind demand teamwork with the Minister of Education, Culture and Science (to strengthen the knowledge base) and the Minister of Economic Affairs, Agriculture and Innovation (to strengthen innovative economic activity).

The above analyses lead to a typology of the clusters with respect to the type of research involved and the government departments that are to play a role in the incentive schemes. This cluster typology is shown in Table 8.

* A correlation of 0 would mean no relationship between market failure and knowledge base. A correlation of -1 would mean a perfect linear relationship between market failure and knowledge base (all points would then lie on a straight line). The correlation that was found of -0.5 means that the linear relationship is small but significant.

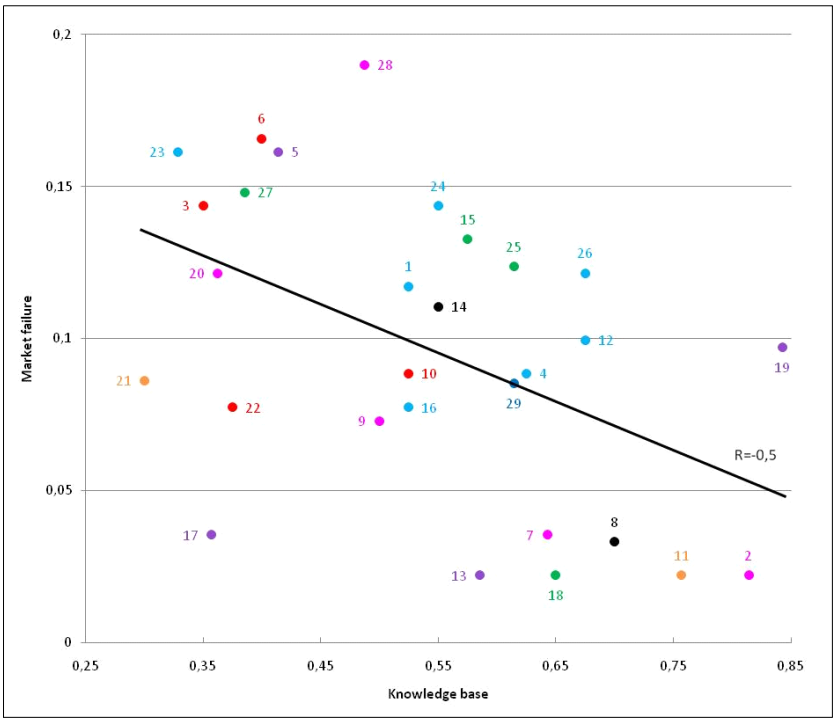

Figure 9 The relationship between market failure and knowledge base. The x axis shows the score for the criterion of knowledge base, with a minimum score of 0.1 (representing a poor knowledge base) and a maximum score of 0.9 (representing an outstanding knowledge base). The y axis shows the score for the criterion of market failure, with a minimum score of 0.022 (representing the absence or virtual absence of market failure) and a maximum score of 0.198 (representing strong signs of market failure). The relationship between market failure and knowledge base is represented by the line (a correlation of -0.5). For the numbers, see Table 6; for the colour coding, see the key to Figure 8.

3.4.3 *Additional themes*

Interviews with experts from academia and industry revealed the groundbreaking trends in research into medical products. Interviews with policy officials at the Ministry of Health, Welfare and Sport identified various needs with respect to major policy dossiers. Many of the developments and needs mentioned in these interviews were also raised by patients and/or care providers. Some examples are personalised medicine, home automation systems (domotics), stem cell therapy and self-diagnosis. In the course of these interviews, however, several important

Table 8 For each cluster the type of research needed, the degree of market failure, the existing knowledge base, and the problem ownership profile.

Cluster (number of products assessed that are in patients' top 3)	Type of research	Market failure (scores between 0.02 and 0.20)	Knowledge base (scores between 0.25 and 0.85)	Necessary partners
A. Regenerative medicine (5)	F + TD	0.02-0.19 (divergent)	0.36-0.81 (divergent)	As a result of earlier investments the initial situation is fairly favourable; the fruits are there to be plucked, but before the harvest the knowledge base will have to be strengthened and expanded. A leading role for the Ministry of Health, Welfare and Sport, the Ministry of Economic Affairs, Agriculture and Innovation and PPPPPs would appear appropriate.
B. Personalised medicine (1; disease-transcending)	F + TD	0.09 (average)	0.61 (average)	As a result of earlier investments the initial situation is fairly favourable; the fruits are there to be plucked, but before the harvest the knowledge base will have to be strengthened and expanded. A leading role for the Ministry of Health, Welfare and Sport, the Ministry of Economic Affairs, Agriculture and Innovation, and PPPPPs would appear appropriate.
C. Medical products targeting effects of disorder (4)	F	0.08-0.17 (fairly large)	0.35-0.53 (fairly weak)	Accumulation of fundamental knowledge and building of infrastructure is necessary: an important role primarily for the Ministry of Education, Culture and Science, and, as Economic Structure Strengthening Fund (FES) partners, the Ministry of Health, Welfare and Sport and the Ministry of Economic Affairs, Agriculture and Innovation, e.g. in a consortium along the lines of NGI. However it should first be investigated whether the knowledge base in other countries is also weak.
D. Improvement of existing medication (2)	TD	0.03-0.11 (fairly small)	0.55-0.70 (fairly strong)	Thanks to a satisfactory knowledge base and distributed market failure, minor incentives (Ministry of Health, Welfare and Sport and Ministry of Economic Affairs, Agriculture and Innovation) should suffice. However further development of the cluster (now 2 scored products) would improve clarity.

E. New medical products targeting disorder (4)	F	0.02-0.16 (divergent)	0.36-0.84 (divergent)	The research involved is mainly fundamental within a heterogeneous cluster (in terms of technology, market failure and knowledge base). The necessary measures and leading parties must be investigated for each product within the cluster.
F. Early, accurate diagnosis involving less discomfort (4)	F + TD	0.02-0.15 (mostly large)	0.39-0.65 (mostly average)	Strengthening and expanding the knowledge base would be fruitful in both the short and the long term. Leading role of Ministry of Health, Welfare and Sport and PPPPPs would appear appropriate.
G. Devices for self-management and self-reliance (7)	(F) + TD	0.08-0.16 (fairly large)	0.33-0.68 (divergent)	Strengthening and expanding the knowledge base would be fruitful in both the short and the long term. Leading role of Ministry of Health, Welfare and Sport and PPPPPs would appear appropriate.
H. Improvement of existing therapeutic interventions (2)	F + TD	0.02-0.09 (fairly small)	0.30-0.76 (divergent)	Thanks to a satisfactory knowledge base and little market failure, minor incentives (Ministry of Health, Welfare and Sport and Ministry of Economic Affairs, Agriculture and Innovation) should suffice. However, further development of the cluster (now 2 scored products) would improve clarity.
I. Home automation systems for remote assistance (-)	TD	No score	No score	N/A.
J. Information processing and information exchange systems (-)	TD	No score	No score	N/A.

F = fundamental research; TD = translational research and development;
PPPPP = public-private-patient-practitioner partnership;
N/A.= unknown, because there was no score for these clusters based on the criteria.

topics were discussed that had not been raised in the course of consultation rounds with patients and care providers.

The first is imaging technology. For nearly all disease areas, this is viewed as an important development. Researchers foresee improvements such as a shift from 2D to 3D and 4D (real time) images, increased resolution, the use of biomarkers in imaging, and reduced radiation. The applications reside in prevention (identifying high-risk groups), diagnosis, and support of invasive therapy and the facilitation of minimally invasive interventions (on the one hand ‘seeing what you are doing’, and on the other hand ‘dry run testing’). The second application (diagnosis) in particular is in keeping with the needs expressed by

patients. This aspect can be incorporated in Clusters F – Early, accurate diagnosis involving less discomfort, and H – Improved therapeutic interventions.

The second important development is decision-support software. Care providers have to deal with large quantities of data about patients' biological functions and biomarkers. In addition many patients take multiple medicines that may interact with one another. Decision-support software can help care providers integrate and analyse all the data. It is also possible to develop (or continue to develop) software for analysing and assessing diagnostic images, on which physicians can base a decision. Software of this kind would have important benefits: standardised diagnosis and less dependence on the subjective eye and experience of a physician; the assessment can be performed by less qualified personnel. This aspect can be incorporated in cluster J – Information processing and information exchange systems.

An important point with regard to IT is that the Minister has excluded software developments from the medical products category. However, those working in the field have often stated that they expect IT to produce many important developments for the care sector. Some examples cited include the above-mentioned decision-support software and systems that care providers need for the exchange of information. But also continued research into biomarkers and the development of personalised medicine are possible only if developments come from IT that facilitate the detection of risk profiles from the large quantities of data generated. In other words, the development of medical products is impossible without simultaneous developments in IT.

The third theme is public health and primary prevention. While these are large policy dossiers, they do not automatically form part of patient surveys. Current areas of concern for the Ministry of Health, Welfare and Sport include resistance to antibiotics, infectious diseases (in particular influenza epidemics), and vaccines. These themes were covered in the 2006 RGO advisory report entitled 'Medical Biotechnology Research Agenda'.[28] The RGO concluded then that prevention should be the Ministry of Health, Welfare and Sport's research priority. The RGO furthermore acknowledged the substantial scale and high quality of research into infectious diseases in the Netherlands (in other words, research into influenza, HIV, tuberculosis, malaria, neglected tropical diseases and resistance to antibiotics). At the time there were various initiatives for promoting infection research and, mindful of the public need, the RGO advocated putting these topics on the international research agenda. The relevance of the RGO's conclusions in 2006 remains undiminished.

The Ministry views the public health and prevention theme in general and infectious diseases in particular as matters of great urgency. The Committee therefore feels that it would be worthwhile to add these subjects to the clusters shown in Table 7:

K. New products aimed at preventing disease and promoting health
L. Improved resources aimed at preventing and treating infections.

The contents of these clusters have yet to be determined by means of surveys of pull parties.

3.4.4 Clusters and long-term vision

Clusters A to L can be used to establish a long-term vision for defining and implementing incentives for the innovation of medical products. For some clusters, it is clear what is needed and which government department should have primary responsibility. However, a more tailored approach is required for other clusters. The urgency of government incentives, and who should be responsible, should then be determined for each medical product.

3.5 Conclusion

The Committee has developed a method for involving users of medical products in the development of a research agenda. This method was applied to fifteen disease areas and has led to usable and sometimes surprising results. The Committee then prioritised the products in accordance with the criteria defined above in Chapter 2. A further analysis led to the identification of ten clusters of products that are important for users. Two clusters were added specifically for the government as a pull party.

This research agenda, which is an answer to the ‘what’ question, is more exemplary than definitive in nature. Users of important disease areas have yet to be interviewed and insufficient justice has been done to some end-users, such as children. The survey of care providers was also limited in terms of scale. This is therefore a work in progress. Aside from the issue of putting it into use, the agenda also needs broadening. The next chapter addresses ways of giving shape to both of these aspects.

Chapter 4

Implementation (the ‘how’ question)

4.1 Introduction

Chapter 2 determined that the Netherlands has an excellent knowledge base, which is capable of acting as a springboard for the development and introduction of innovative medical products. In combination with the Ministry of Health, Welfare and Sport’s public responsibility for improving health and care, this provides an obvious justification for investing in medical products research. Chapter 3 then listed those medical products that need to be developed from users perspectives. This led to a specific agenda. This final panel of the triptych sets out ways in which the agenda can be implemented.

Innovative medical products do not appear out of thin air. Many factors help or hinder the actual translation of knowledge into products that reach the patient or the public. In addition to targeted investment in research, which is the subject of this document, there were a number of other relevant points. These include the propensity to issue patents and to engage in technology transfer; regulations surrounding clinical research; the procedures for admission to the market; and the decision process for inclusion in the range of reimbursable products. A balance must constantly be found between the justifiable desire for rapid innovation of our current range of products, and the need to proceed with due care when dealing with people and funds. Other advisory reports and memorandums have comprehensively addressed this point.[2,16,17,20,22,29-34] This document restricts itself to answering the question of how the Ministry of Health, Welfare

and Sport, possibly together with other ministries, can promote the research and development needed to produce medical products that users consider valuable.

4.2 Method

The Committee dealt with the Minister's question – how to promote research into medical products – as follows. Firstly several lessons for successful innovation are drawn from innovation theory, previous investigations (Section 4.3) and five cases (Section 4.4). These lessons are translated into conditions for success that could be shaped by the government's incentives policy (Section 4.5). The necessary government contribution, in the form of incentives and facilities, is discussed in Sections 4.6 and 4.7, respectively. Section 4.8 describes how the research agenda can be dynamic while also providing a basis for long term research policy. The conclusions are set out in Section 4.9.

4.3 Innovation and collaboration

4.3.1 Innovation theory

This section refers back to Figure 3 in Section 2.4, which introduced the innovation system and its most important players. Whereas innovations would once have tended to be generated within individual organisations, it is now more usual for new products and processes to be developed jointly with other parties. This external orientation (teamwork) has been necessitated by factors such as ever shorter product life cycles, the focus on highly specialised knowledge, and pushing the boundaries of technologies to arrive at new innovations.[35] In addition, the pharmaceutical industry in particular is affected by an 'emptying pipeline' – in other words a declining number of products for which a company has patent rights.[36] Industry is therefore constantly in search of new partners: in balanced joint undertakings, but often also in the form of mergers and acquisitions.

Joint venture partners allow organisations to access fresh knowledge and technologies sooner and more effectively than if they were to restrict themselves to their own organisation. These joint venture partners, as the innovation system shows, can range from companies research institutions, and users, to name but a few (see Figure 3). Section 4.3.2 will discuss details of collaboration between push parties, while Section 4.3.3 will address collaboration with users (pull).

4.3.2 *Collaboration between push parties in the Netherlands*

In 2008, the Ministry of Health, Welfare and Sport engaged the Rotterdam School of Management to identify innovation success factors in the life sciences and medical technology sectors by surveying a random sample of Dutch companies. The survey showed that innovation success is determined not only by investments in research and development. Significantly, it is also shaped by organisational aspects (the style of working and of management); in other words, 'social innovation' (see Box 3).[31]
s

Box 3 Social innovation is defined as:

1 flexible organisation: combining innovation and efficiency activities; horizontal teamwork; shared decision-making;
2 dynamic management: experienced management team with varied backgrounds; visionary leadership; group rewards;
3 external teamwork: intensity and diversity of external partnerships.

These factors put organisations in a position to rapidly identify, digest and apply new knowledge (capacity for absorption).[31]

The Rotterdam report observed that the return from R&D investment in the Dutch life sciences and medical technology sector was relatively low, and could be improved mainly by working on management qualities, leadership and, above all, by acquiring experience of partnership. International rankings produced by the World Economic Forum also show that the Netherlands still scores poorly in terms of social innovation.[18]

Accordingly, there is room for improvement in the collaboration between push parties in the Netherlands, and this area is now receiving attention. Various publications have urged collaboration and the creation of clusters in the life sciences and medical technology.[37,38] The government also attaches importance to the creation of focus and mass. In recent years, therefore, it has been providing increasing incentives (as finance co-provider) to the formation of consortia involving various parties from different backgrounds. Experience gained in recent years with this type of partnership has shown that improvement is possible.

Firstly it appears in practice that top-down initiated partnerships in the consortia tend to disintegrate when the financial incentive is removed. In other words, partnerships are not always very resilient. But why should this be? Communication and trust appear to be important conditions for successful collaboration. Contacts or past collaboration may help, as those involved will be familiar with each other (communication) and will therefore know what to expect (trust).[31] If the only motivation for collaboration is the acquisition of research funding, then it will be unlikely to stay the course.

With this in mind, the NWO Innovative Medical Devices Initiative Netherlands (IMDI.nl) programme took an unconventional approach to the formation of consortia. From the outset, NWO-IMDI envisaged institute formation between parties from different backgrounds (UMCs, Universities of Technology, other knowledge institutes, companies and care institutions). The initiatives came from research groups within the institutions, but the executive boards of these institutions also made contractual commitments to the newly formed institute. This approach explicitly acknowledged the independent authority of the executive board of the new institute and facilitated administrative embedding. The founding organisations were also required to produce business plans to show that they would generate a return on investment. The institutes formed during the past one or two years, without any certainty of acquiring government funds. NWO hopes to be able to acquire funds for the IMDI institutes, based on a strategic vision presented on 18 November 2010. NWO foresees the structural expansion of research and development activities in the consortia that have been formed through a one-off incentive with a sufficiently long term (ten years is envisaged).

A second area of concern in current consortia is the lack of involvement of end-users. Knowledge institutes and industry are obvious consortia parties, while users (the pull) are not usually at the table. Some users are medical specialists, and may be involved as researchers. However, other users, such as nurses and patients, are seldom full parties in these research programmes. Collaboration with the pull is discussed in the next section.

4.3.3 Collaboration with end-users (pull)

At least five reasons are given in the literature for involving users in the innovation process: 1) they are aware of the need (agenda setting); 2) they have experiential knowledge; 3) their involvement may increase the cost-effectiveness and performance of the R&D process; 4) they may help reduce any public

resistance; and 5) their involvement gives legitimacy to public research funding.[39-41] In the case of medical products, the users in question are patients and care professionals.

There are various degrees of involvement, which is also referred to as participation. The rungs of what is known as the participation ladder are: informing; consulting; advising; co-producing; and deciding. The higher up the participation ladder, the greater the influence of the users involved. However, the objective is not necessarily to position users as high up the participation ladder as possible in the development process. The degree of participation must be appropriate to the activity and the objective being pursued. Two possible user roles are described on the basis of two key functions in the innovation system – knowledge development and search.[19]

Knowledge development is a key process in innovation theory that consists not only of learning through research (research and development), but also of experiential learning, or learning in practice.[19] Users are naturally of great importance in this respect. Patients have long been involved in clinical trials as test subjects, but they have had hardly any influence in this role: they merely provide information. However, users' experiential knowledge has proved to be interesting and relevant in applied research, product development and fundamental biomedical research alike. Users' empirical knowledge is supplementary (explication of and reflecting on repeated experience) to scientific knowledge (argumentation, experiments and observations).[42] The involvement of users in medical and biomedical research as advisers, co-producers or even decision makers, can be extremely valuable, as the RGO has stated before.[25] The Duchenne Parent Project case also made this point convincingly (see Section 4.4). This document does not explore the role of users in knowledge development.

A second key function in the innovation system is 'guidance of the search'. This centres on making wishes, needs and expectations explicit.[19] Users of medical products are almost indispensable in this endeavour. This advisory report indicates a method for specifying this user contribution to innovation. Patients were requested to produce a top 3 of desired products in their own disease area. Involving patients in knowledge development is further developed than involving users in agenda setting. The aim is not the representation of interests, nor being involved in decisions, but acquiring sound empirical knowledge from the users. How this aim should be achieved depends on the precise circumstances, and requires a structural and purposeful approach: who should be

invited to participate, to what extent, and which participation method should be used.[25,43-45]

4.3.4 *Summary of innovation theory*

Collaboration is a key word in innovation theory. However good the scientific research and the resultant knowledge base, collaboration between individual researchers and developers and between researchers/developers and users is of pivotal importance. Without this, no new products will be produced at the pace and of the type that the public needs. Collaboration demands courage; knowledge and control have to be shared. The art is to produce stable continuous partnerships that are also sufficiently open to accommodating new developments and entrants.

4.4 Collaboration: successful practical examples

The Committee investigated five practical examples of partnership with a view to identifying lessons to be learned. All the initiators of these five partnerships came from different parts of the innovation system: care providers (researchers/physicians (HOVON)); parents of patients (Duchenne Parent Project); a funding body (the Dutch Kidney Foundation, with the implantable artificial kidney); a company (Philips); and a government (of the United States, (HAART)). There is a more extensive analysis of each case (of strengths, weaknesses, opportunities and threats) in Annex I.

4.4.1 *HOVON*

The Haemato Oncology Foundation for Adults in the Netherlands (HOVON) is an alliance for haemato-oncology in the Netherlands. It also has a Belgian branch. HOVON's objective is to develop, initiate and implement prospective studies among patients with malignant haematological disorders in the Netherlands and Belgium. The ultimate goal is to improve the diagnosis and treatment, care and quality of life of patients with malignant haematological disorders (such as leukaemia and lymphoma).

The foundation was formed in 1985 through a special collaboration between the haematology departments of the eight university hospitals and several major non-teaching hospitals, in the awareness that the prospects for leukaemia and lymphoma patients could be improved only through high quality studies, for which collaboration would be indispensable.

These studies were performed by working groups that focused on a specific disorder, or on technical aspects, such as those related to diagnosis. The HOVON data centre (HDC) is responsible for all practical matters involved in performing trials, and monitors the quality of the centres that participate in studies.

HOVON has links with university and medical researchers in the Netherlands and far beyond. HOVON also works with the pharmaceutical industry, e.g. in phase I-III trials. In recent years contact has been made with patients' organisations, in particular in view of similar lobby objectives. However, HOVON is now seeking opportunities to bring about user involvement in agenda setting and research.

Since its formation, HOVON has performed more than one hundred trials with internal resources (i.e. with no direct government subsidy). Many of these trials have been reported in prestigious journals, such as Blood. By incorporating the trials results into evidence-based guidelines, HOVON has succeeded in rapidly applying research findings in the everyday diagnosis and treatment of haemato-oncology patients Another important impact of HOVON is that relatively small hospitals are also able to participate in trials, thereby improving the quality monitoring of their research infrastructure and the quality of care for all patients with malignant haematological disorders in these hospitals. The HOVON trials have contributed to the fact that in 2010 leukaemia and lymphoma are no longer a death sentence.

4.4.2 Duchenne Parent Project

The Duchenne Parent Project (DPP) was started in 1995, at the initiative of a mother of a boy with Duchenne muscular dystrophy. They attended a conference in the United States at which parents asked researchers what they could do to help put Duchenne research on the map. The researchers replied that what was really needed was adequate funding . DPP was then set up in the Netherlands, to raise money for research.

DPP's organisation can be described as lean and mean. DPP has no office and operates entirely through the efforts of volunteers. DPP is an open organisation, and all parties sit around the table: government; industry; the academic world; and patients and their parents.

DPP is oriented to providing information about neuromuscular disorders and fundraising for research, which it does through a variety of cultural and sports activities. The money collected for research (approximately 1-2 million euros a year) is allocated by means of a rigorous peer review procedure. Research that is funded is oriented to finding a cure for Duchenne. DPP has for fifteen years

succeeded in raising sufficient funds for research into Duchenne treatment. Exon skipping – a form of gene therapy – is an example of a treatment that could have been developed thanks to DPP funds, and which is likely to become available to patients in the near future.

4.4.3 *Implantable artificial kidney*

The Dutch Kidney Foundation's mission is to create a future with as few kidney diseases as possible and better prospects for kidney patients. The health fund is committed to better and more effective treatment methods and a better quality of life for kidney patients. One of the ways of contributing to the mission is to invest in scientific research.

In recent years dialysis treatment development has contributed little to improving the quality of life of kidney patients. Regeneration of the patient's own kidney or making a tissue-engineered kidney (regenerative medicine) is not possible at this stage. One medium-term option is a portable, or even implantable, artificial kidney. The Dutch Kidney Foundation has pointed out that the Netherlands has ample expertise to achieve this objective. The health fund has devoted much time, energy and funds to this vision of the future. There are now two active Dutch consortia: one for the development of a portable, non-biological artificial kidney; and one for a biological (portable or implantable) artificial kidney. The latter consortium is financed by the BioMedical Materials (BMM) programme. The first steps on the path to a greatly improved artificial kidney have been taken. The Dutch Kidney Foundation expects the goal of a portable or implantable artificial kidney to be achievable within ten years.

Based on patients' needs, the Dutch Kidney Foundation has outlined a clear and promising future perspective. It has also succeeded in attracting the interest of the academic world and industry for the necessary development work. The Dutch Kidney Foundation is a natural hub in the network of patients' interests and in research funding, and is thereby able to forge a link between push and pull.

4.4.4 *Innovation management at Philips*

In recent years Philips has concentrated increasingly on the healthcare and wellbeing sectors, with products such as: imaging technology; home health care; patient monitoring; and clinical decision support.

Philips has drastically revised its innovation process to market products of this kind. Actual obstacles in the care field form the starting point for identifying

technological solutions (instead of ‘creating demand’, as was the case with the CD and other developments). To this end, Philips maintains an extensive network throughout the development process. Contacts run through various channels. There are consumer panels (e.g. members of the public about prevention, or physicians in peripheral hospitals) and service centres (customers), as well as interviews (patients), contacts with umbrella organisations and health funds, and open platforms such as ehealthnu.nl.

For specific diseases the entire ecosystem surrounding the patient is mapped out. The main obstacles perceived by patients and care providers are investigated, while soliciting their views on how to improve the care process. The experience and ideas of users provides Philips with inspiration for product development based on current or new technologies. The exact target group of a new product becomes increasingly clear during the innovation process. As a result, interaction in later phases is increasingly oriented on, and in collaboration with, this target group. In this way, the technology and the product are developed further with the objective of eliminating obstacles observed during the development process, and of guaranteeing effective implementation of the solutions. Many projects of this kind take place in an Open Innovation setting, to achieve maximum and sustained interaction between participants.

4.4.5 *Therapy for people infected with HIV: HAART*

The final case is an international programme largely initiated by the US government. In the early 1980s a previously unknown disease emerged that was later given the name AIDS. The United States Congress arranged for $15 million in research funding. Major scientific journals such as Science and the New England Journal of Medicine also gave priority to articles about AIDS. When the cause of AIDS – the Human Immunodeficiency Virus (HIV) – was discovered, the National Cancer Institute (NCI) set up a special task force on AIDS, with the objective of finding a therapy (1984).

At the initiative of the Clinical Director, industry was also directly involved. Fifty companies supplied substances that, for property rights reasons, were subjected to blind testing. Burroughs Wellcome (BW) supplied azidothymidine (AZT), which had previously been found to be effective neither against cancer, nor as an antiviral agent for widespread use. AZT appeared to work against versions of HIV in mice, by inhibiting the viral enzyme reverse transcriptase. A patent was filed and the necessary animal and clinical trials were initiated. All of the above stages were completed with great rapidity. The Food and Drug Administration (FDA) worked at unprecedented speed, and the NCI supplied

additional thymidine and laboratory space. Soon after the start of phase II (double-blind randomised) trials, the agent appeared so effective that it would have been unethical to withhold it from the patients in the placebo arm of the trial. A registration file for Retrovir (the brand name for AZT) was prepared for the FDA, with approval of the medicine following in early 1987. In the meantime, AZT had been distributed free of charge.

After registration, BW demanded a high price for Retrovir. The lesson carried forward to subsequent partnerships between government, the academic world and industry was to establish clear price agreements in advance. For example, this was achieved with dideoxyinosine (ddI), the second medication for HIV/AIDS, by means of a 'reasonable price clause'.

Besides antimetabolites such as AZT and ddI, which inhibit viral reverse transcriptase, industry independently developed protease inhibitors in the 1990s (indinavir/Viramune; ritonavir/Norvir; saquinavir/Invirase). The current HIV/AIDS therapy comprises a combination of two reverse transcriptase inhibitors and a protease inhibitor, known collectively as HAART (highly active anti retroviral therapy). This therapy is often supported by medication that strengthens the immune system, but does not specifically target HIV.

4.4.6 *Summary of practical examples*

The HOVON case shows how collaboration between care providers in teaching and general hospitals can raise the national standard of care to a higher level. HOVON is open to partners (other than the care providers) who are able in some way to contribute to this objective, such as industry and patients' organisations.

The Duchenne Parent Project shows what can be achieved with determination and drive. It also demonstrates that patients too can play a valuable part in the innovation system.

The Dutch Kidney Foundation has also shown tenacity and ambition. This health fund divided the ambitious ultimate target into feasible intermediate targets, which helped it to unite relevant push parties behind this pull requirement.

Philips has succeeded in redirecting its innovation process from 'creating demand' to 'satisfying a need'. The case shows that the contacts with users were indispensable to this success.

The HAART case shows the feasibility of effective collaboration between the academic world and industry. It also proves that government can have a crucial facilitating role, by making available substantial financial resources and by

eliminating bureaucratic obstacles to innovations that have considerable public health and care potential.

4.5 Lessons from theory and practice: conditions for successful collaboration

A summary of the conditions for successful collaboration on the development of innovative medical products, as derived from theory and practice, is given in Box 4. This identifies the building blocks needed to implement the medical products research agenda. The following sections add specific details.

Box 4 Conditions enabling successful partnerships to achieve medical product innovation:

1 Willingness to put needs at centre stage (central role of users)
2 Skill in internalising experiential knowledge of users (patients and care providers) through professional dialogue in the innovation process
3 Inclusion of users (patients and care providers) as full joint venture partners*
4 Substantial drive, primarily by the party that took the initiative (broader than individual initiators)
5 The courage to think outside conventional (and traditional) approaches
6 Prior partnerships (communication and trust)
7 Openness to all possible relevant partners (however unconventional they may be)
8 Having a joint objective (realistic and measurable at intermediate stages, possibly divided into feasible milestones) and creating clear agreements
9 An effective organisation (short communication lines, little bureaucracy)
10 Sufficient financial funds (without much uncertainty and/or fluctuations)

* see the 2007 RGO advisory report about user involvement.[25]

4.6 Incentives from the Ministry of Health, Welfare and Sport and partners

Collaboration is a common theme in the theory and practice of successful product development. If the knowledge base is satisfactory and push parties are able to find each other, two important conditions for successful innovation will have been met. This advisory report adds a new dimension, in the form of users' experiential knowledge for the purpose of agenda setting. This experiential knowledge is important, because it keeps the researchers and developers alert. Not everything that is interesting from the push perspective is relevant for users. Strengthening the input from users can help improve the efficiency of efforts on the most important issues of care policy: quality; accessibility; and affordability.

The 'how' question could therefore be translated for the Minister as "How can I use experiential knowledge to align the development of medical products better with my responsibility for quality, accessibility and affordability?". In order to answer this question, in Section 4.6.1 the Committee scrutinises existing partnerships and programmes in the specific area of research into new medical products and their development. This adds detail to the exercise in Section 2.4, which broadly examined Dutch life sciences research.

4.6.1 Medical products development in the Netherlands

The Netherlands is very active and successful in research in the medical and biomedical fields, as was observed in Chapter 2. There is collaboration between push parties in countless areas, occasionally also involving users. Table 9 – without pretending to be complete – gives examples of existing structures and programmes that are completely or partially oriented to research into or the development of medical products. The right-hand column shows the medical product or cluster of products for which the structure concerned would be a good base. Instead of adding new structures, the Committee considers it preferable to identify opportunities for allowing users to put forward their experiential knowledge in a structural and continuous way, to influence the agenda setting of these partnerships and programmes. In other words: the collaboration between push parties within the existing structures is largely in order, and now the link with the pull parties must be attended to.

Table 9 shows that no single existing partnership or programme covers the entire breadth of medical products (pharmaceuticals, tissue-replacement products, and devices for diagnosis and care) or the entire breadth of disease areas. Together they provide almost complete coverage of the medical and biomedical field of development, but it is no easy matter to obtain a satisfactory overview. In the opinion of the Committee, the challenge is not to establish new structures, but to make better use of the existing programmes. A link must be made between these existing structures, which are usually funded by the government itself, and the objective of orienting medical product development better to the user perspective. What tools exist or must be developed?

4.6.2 *Subscribe to funding of medical product development and related testing*

Tables 5 and 7 in Chapter 3, which shows the products (Table 5) and clusters (Table 7) mentioned by the pull can be set alongside Table 9, which shows the research programmes and partnerships: which groups could be engaged on which products or clusters of products?

Table 9 Examples of existing structures oriented to medical products research.[a]

Existing structures	Oriented to	Suitable for
National public-private partnerships (translational, precompetitive research)		
TI Pharma	pharmaceuticals	Pharmaceuticals, distributed across Clusters B, C, D and E
Centre for Translational Molecular Medicine (CTMM)	molecular diagnostics, imaging, targeted interventions	Cluster B (personalised medicine); Cluster F (diagnostics); Cluster H (improved therapeutic interventions)
BioMedical Materials (BMM) programme	tissue-replacement products	Cluster A (regenerative medicine)
Sector LSH (toward value creation through an integrated infrastructure)	broad (pharmaceuticals; diagnostics; tissue-replacement)	various clusters: research in translational phase (with much attention to stem cell/tissue engineering research)
Top Institute for Healthy Ageing (Ti-GO)	early detection (prevention), enhanced self-reliance, individual health management	in particular Cluster G (self management and self-reliance)
Netherlands Genomics Initiative (NGI)	genomics technology	Cluster B (personalised medicine) and Cluster F (diagnostics), where oriented to biomarkers
NanoNext NL (towards a sustainable open innovation ecosystem)	microtechnology and nanotechnology (implementation of Strategic Research Agenda of the Dutch Nano Initiative; NNI)	Cluster B (where oriented to targeting the medicine) and Cluster G (where oriented to home diagnosis)
NanoLab NL	nanotechnology (implementation of NNI Strategic Research Agenda)	Cluster B (where oriented to targeting the medicine) and Cluster G (where oriented to home diagnosis)
NIH&C	cognitive processes	medical products related to cognitive disorders (depression, anxiety, dementia)

European public-private partnerships (translational, precompetitive research)		
Innovative Medicines Initiative (IMI)	Pharmaceutical development	Pharmaceuticals, distributed across Clusters B,C,D and E
National public research programmes		
NWO: IMDI.nl	• two CoREs oriented to extramural diagnosis, monitoring and treatment • four CoREs oriented to imaging (imaging and image analysis) • one CoRE oriented to minimally invasive technologies one • CoRE oriented to diagnosis and treatment of neurological disorders by means of neuroplasticity	• Cluster G (self-management and self-reliance) and Cluster I (domotics) • part of Cluster F (diagnostics) • Cluster H (improvement of therapeutic interventions) • Neurobiological products for dementia, CVA, depression and anxiety disorders (mostly Cluster E)
NWO: nanotechnology	nanotechnology (implementation of NNI Strategic Research Agenda)	Cluster B (where oriented to targeting the medicine) and Cluster G (where oriented to home diagnosis)
ZonMw: Ambient Assisted Living	technological/IT products, services and systems (in the light of population ageing and shortage of personnel)	primarily Cluster I (domotics), but also Cluster G (self-management and self-reliance)
ZonMw: Diabetes	research into diabetes, part of which is medical products	medical products related to diabetes
ZonMw: *Geestkracht*	research into anxiety and mood disorders, psychoses and behavioural disorders	medical products to treat such things as anxiety disorders and depression
ZonMw: Healthy nutrition	research into healthy nutritional patterns, possibly with functional foods	medical products related to nutrition, as expressed by patients with dementia and gastrointestinal and liver disorders
ZonMw: Insight	research oriented to improving quality of life of people with a visual impairment	medical products for visual impairments
ZonMw: National care for the elderly programme	research into care for elderly people with complex care needs. Elderly people themselves have an important voice. Not primarily oriented to medical products.	medical products for prevention, diagnosis and treatment of disorders in elderly people
ZonMw: Palliative care	research into improving palliative care. Not primarily oriented to medical products	Cluster C (consequences of disorder), in particular pain control
ZonMw: Priority Medicines	research into pharmaceuticals for children and for elderly people and pharmaceuticals for antimicrobial resistance and rare disorders	Cluster D (improved medication), Cluster E (new medical products to combat disorder) and Cluster L (anti-infection agents)
ZonMw: Translational research	adult stem cell research and gene therapy research	Cluster A (regenerative medicine)
ZonMw: Orphan drugs	pharmaceuticals for (diagnosis, prevention, treatment of) orphan diseases	pharmaceuticals related to rare disorders
ICT-Regie[b]: IT Innovation Platform ‘Health support’	IT research oriented to improving quality of life; quality of care; and personalised care	Cluster G (self management and self-reliance); Cluster I (domotics); and cluster J (Information processing and information exchange systems)

ICT-Regie[b]: IT Innovation Platform 'Brain & Cognition'	IT research in relation to neurocognition research	specific medical products within Cluster G (self management and self-reliance), such as brain-computer interfaces, biofeedback, and deep-brain stimulation
ICT-Regie[b]: IT Innovation Platform 'Domotica & Smart Living'	IT research	primarily Cluster I (domotics), but also Cluster G (self-management and self-reliance)
Technology Foundation STW: Perspective CARISMA (Cardiovascular Risk Management)	analysis methods of complex imaging to improve diagnosis, treatment and prognosis	medical products for cardiovascular disorders
Technology Foundation STW: Perspective GenBiotics	new genomics-based antibiotics	Cluster D (improved versions of existing medication)
Technology Foundation STW: Perspective NeuroSIPE	diagnostics for neurological disorders	medical products for neurological disorders
Technology Foundation STW-Danone partnership programme	• understanding process from ingredient to specialised nutritional product • understanding role of gastrointestinal tract in neuroimmune modulation in sickness and health	Cluster E (new medical products oriented to disorder), where oriented to nutrition
Technology Foundation STW/ Foundation for Fundamental Research on Matter (FOM)/Nanoned: National Nano Initiative)	nanotechnology	Cluster B (where oriented to targeting medication). Cluster F (early, correct and less invasive diagnostics) Cluster G (where oriented to home diagnosis) Cluster H (improved therapeutic interventions)
European public health programmes		
7th Framework Programme	Health (broad)	Various clusters (a different focus each year)
Health funds		
Association of Health Funds (SGF) (with ZonMw)	research into comorbidity from a disease-transcending approach	no specific cluster
Individual health funds	incentives for research within a specific disease area	medical products for specific disorders
Disease-oriented cooperative groups for clinical research		
HOVON	research into treatments for malignant haematological disorders	medical products for malignant haematological disorders such as leukaemia or lymphoma
Duchenne Parent Project	research into treatments for Duchenne	therapeutic products for specific muscular disorder (Duchenne)
The Netherlands Heart Institute (ICIN)	research into (treatments for) cardiovascular diseases	medical products for vascular wall and myocardial disorders.

a The left-hand column shows the partnership or programme, the centre column the objective of the partnership or programme, and the right-hand column the medical products or cluster of medical products for which the partnership/programme could be suited. The examples given have diverse budgets and terms. This list does not pretend to be complete or entirely up-to-date.

b ICT-Regie ends in 2010.

These groups could then be asked to identify those products or clusters to which they would wish to subscribe. These activities are compatible with the tools 'addressing and agenda setting' and 'binding and collaborating' that the Care Innovation Platform envisages for stimulating innovation.[22]

In order to judge whether it is sensible to have targeted incentives for research questions by certain groups, it is worthwhile first subjecting the group to a group assessment and a product assessment.

The group assessment uses the conditions for successful collaboration (see Box 4). This measuring tool addresses three specific aspects for setting the agenda for medical products:

1 The group is willing for the agenda setting to be influenced in a professional way by the wishes and needs of users. This can lead to public-private-patient-practitioner-partnerships (5Ps).
2 The collaboration is demonstrably good (track record) and the partners are open to new relevant partners.
3 The group demonstrates an actual capability of developing new products; not stopping with knowledge development.

The product assessment uses the experiences and the method proposed in this document. The Committee has experimented with methods for converting medical products needs of patients, physicians, nurses and informal carers into an agenda. This demands consultation, followed by prioritisation. Based on this experience, a product must satisfy the following:

1 The survey of users revealed the need for the product to be developed.
2 The product development has priority in view of its significance for the quality, accessibility and affordability of care (weighting in accordance with Criteria 1-4 given in this document).
3 The product would be developed too slowly, or not at all, in and by the market (Criterion 5).

Group assessment and product assessment can be used to assess group subscriptions to projects involving the targeted stimulation of product development. The link between push and pull, which an assessment of this kind guarantees, should lead to targeted financial subsidies by the Ministry of Health, Welfare and Sport based on a new 'Innovative Medical Products' meta-programme.

In this context use can also be made of the findings and recommendations in the advisory report entitled *Value for our money. Deciding on public investments in health research*. Decisions on public investment in health research, where

methods are discussed that can be used in decisions about the scale and promise of investments in the development of specific products.[46]

4.6.3 New initiatives

If medical products, or even clusters of medical products, are not taken into development within the existing structures, then new initiatives must be created. This could be the case with Cluster C – new medical products oriented to the consequences of the disorder. Much fundamental research is needed within this cluster, the current knowledge base is still unsatisfactory, and the market failure is substantial. It is therefore very likely that this cluster cannot be 'positioned' within the existing structures. A situation of this kind can also occur with individual medical products in other clusters.

In such cases, the government, possibly together with other public and private parties, should create a new initiative for the cluster or individual medical product concerned. It is anticipated that resilient new partnerships (see Section 4.3.2) will be established. These could be designed along the same lines as the IMDI.NL institutes that are currently being set up, with the exception that the pull must be more heavily involved. The new initiatives must then also – as described above – pass the group assessment and product assessment. Furthermore, it must be assessed whether financial investment is the most appropriate remedy for the market failure.

4.6.4 Financial incentives

Research into a new medical product has a clear ultimate objective: application, if feasible, of the product in the care sector. This means that milestones in the research can be set, and that funding can be linked to achieving these milestones. The Netherlands Organisation for Health Research and Development (ZonMw) has experience of the Translational Gene Therapy Research and Translational Adult Stem Cell Research programmes. The research in both programmes is divided into phases, each of which has a fixed duration and a defined amount of funding. If the milestones for the first phase are achieved, the research passes to the next phase, with a follow-on budget and a new timescale. If the milestones for a phase are not achieved, the researchers must catch up with the milestones with their own time and funds in order to claim the budget for the next phase. This research funding method guarantees focus and budget for the full duration in which the product development should reasonably occur. The relatively long duration of the programmes (8 years) is an important factor.

4.7 Government facilitation

The funding of medical and biomedical research and product development is complex, as was shown in Figure 3 in Chapter 2, and again clearly illustrated in Table 9. The most important financing parties are: the Dutch government (Ministry of Education, Culture and Science, Ministry of Health, Welfare and Sport, Ministry of Economic Affairs, Agriculture and Innovation, public funding agencies); Europe; industry; health funds and other charitable organisations; and health insurers. These parties have widely varying interests with regard to the creation of innovative medical products, or to the relevant agenda (drawn up in Chapter 3). Sometimes the research into and the development of a medical product proceeds rapidly and satisfactorily because interests are large or congruent, and at other times progress is slow or in the wrong direction because important parties see no benefit, or are on different wavelengths. Where, necessitated by market failure (a mismatch between supply and demand), the government resorts to active financial incentives, it could also be the case that earlier or better consultation of lay experts would have given rise to parties other than the government focusing more on prioritised medical products. It is therefore conceivable that the research that is supported by the health funds, charitable organisations and insurers becomes more sharply focused on the development of products that are relevant to users. The Netherlands Bureau for Economic Policy Analysis (CPB) has produced a memorandum entitled *Choices in innovation policy: building blocks for the review working group on Innovation and Applied Research*. This states that the government should only intervene where there is persistent market failure and where the economic benefits of intervening outweigh the public costs involved. Funding as a tool is mainly appropriate when there are ‘knowledge spillovers’ (fewer opportunities of market exclusivity because the knowledge required for the innovation is generally accessible), or capital market problems because the risks for the investors are hard to determine. Where monopoly positions or handicaps for new start-ups exist, legislation and regulations are the most appropriate measures.[47]

As shown in this document, surveying users is an intensive exercise that must be performed in a professional way. It is therefore undesirable for every party involved in product development to conduct their own consultation. The professionalism to do so satisfactorily will often be lacking, patients and care providers will become overloaded, and conflicting findings will lead to awkward discussions. It is preferable for these surveys to be conducted in a coordinated

manner. This document proposes a generally usable method for surveying patients, physicians, nurses and informal carers.

The government has an important role in facilitating these surveys. Without this, the service will be performed in an ad hoc way and, on occasion, they may not be entirely free of vested interests. A sufficient budget could encourage those working in the field to take the initiative. Furthermore the budget would also enable patients' organisations, which are often short of funds, to be the party with the initiative.

The budget is needed mainly for the appointment of an independent facilitator. Two requirements that a facilitator* must satisfy are to have: no interest in the outcome of the survey; demonstrable expertise in surveying patients or care providers.

It is precisely by making funds available that the government can set these conditions on the survey process.

4.8 Keeping the agenda dynamic

The Minister requested the RGO to consider the question of how the research agenda can be the basis for long-term research policy. He also requested an indication of how the agenda can be kept up-to-date in the face of changing priorities change and advancing scientific and technological insights.

Since the research agenda presented here is a work in progress, it clearly must be kept dynamic. Tools were proposed in the above sections to help achieve this aim.

The Minister may task an organisation to be appointed by him to survey patients about other disease areas, in accordance with the methodology presented in this document. In this way the clusters can be refined systematically and under central control.

The Minister may make a budget available to those working in the field that wish to conduct the patient survey for a specific disease area. The subjects must then be partnerships of pull and push, supported by a third party with experience of patient surveys. Details can then be added to the clusters decentrally under the responsibility of those working in the field.

Disease areas that have previously been the subject of patient surveys (e.g. the ones surveyed in this report) could be updated by means of broad patient surveys on Internet. This exercise would be less time consuming than holding

* What is meant is a professional organisation with experience in the area of surveying patients and groups of care providers.

focus groups. For instance, it could be established fairly simply whether priorities identified earlier are still needed, and whether any new needs have arisen.

Although the research agenda is a work in progress, it can be used for medium and long-term research policy, since the clusters indicate which areas represent the greatest need for medical products. Furthermore, it is clear for many clusters what specific knowledge and technology development is needed. It is therefore expected that the clusters will remain up-to-date for between eight and ten years, even if details of specific products change more rapidly. If evaluation after five years reveals that the strategy was successful, the method used in formulating this advisory report could be repeated in eight to ten years' time, with the purpose of identifying clusters that are relevant then.

To recap, the twelve clusters presented here (together with the attendant knowledge and technology development) are expected to remain up-to-date for the next eight to ten years. In this period dynamism must materialise within these clusters. After this period it would be advisable for the government to have a new research agenda drawn up with the objective of identifying the then relevant clusters, but, needless to say, only if preliminary evaluation indicates that implementation of the present agenda has led to success.

4.9 Conclusion

Collaboration appears to be a key word for achieving successful innovation. This observation can be drawn from a summary of innovation theory and analysis of several practical examples. There are many partnerships in the Netherlands involved in medical and biomedical research. This research has the potential to be translated into innovative medical products. What is missing is a structural and professional contribution from the perspective of the end-users. There are two ways in which this contribution can be achieved:

- targeted financial incentives for research groups that are willing in their research to embrace the prioritisation of medical products through surveys of users; a method for the 'embracing' is given in this document
- targeted facilitation of surveys of users. It is important for the output of these surveys also to be made available to research finance providers other than the government.

Both aspects can be incorporated into a 'Innovative Medical Products' meta-programme.

Chapter 5

Recommendations

Patients and care providers in the Netherlands need new medical products, so research in this area must be encouraged. Furthermore, this country has a sufficiently good knowledge base to enable it to successfully work on their development. One factor is of particular importance: the match between the capabilities of science and industry and the needs of end-users. This document aims for this compatibility by describing how to draw up and implement a relevant research agenda for innovative medical products. Based on the Committee's work and analysis the RGO gives recommendations in this chapter with the objective of easing and ensuring the success of the above-mentioned match.

Main recommendation

Set up an 'Innovative Medical Products' meta-programme. This meta-programme would be superimposed over the existing research programmes and projects. It would have two purposes, firstly to help organise consultations with users and secondly to encourage research that focuses on the results of these consultations.

The idea is for this meta-programme to act as a catalyst in the research. The existing programmes are the motor, and will be given a boost in this way. The following additional recommendations may be made based on the Committee's experiences regarding both of the meta-programme's instruments – facilitation of surveys, and incentives for research oriented to the survey output.

Recommendations concerned with surveys

> Facilitate national consultations with the users of medical products, according to the method set out in this advisory report.

The RGO hereby also recommends the following. The surveying of users demands a professional and independent approach. An arbitrary selection of respondents and suggestive phrasing of questions should be avoided. This is the reason for preferring a controlled and national approach. An approach of this kind must satisfy several conditions:

- the surveys must take place under the supervision of an independent facilitator
- the facilitator must have no interest in the substance of the outcome
- the facilitator must have experience with this kind of survey.

The survey output will be valuable, but also voluminous and diverse in nature. The RGO therefore recommends the following:

> Rank the results of user consultations using a scoring and evaluation system, as set out in this advisory report.

Recommendation concerned with incentives

> Have partnerships subscribe for additional funds for development of medical products that are prioritised within the 'Innovative Medical Products' meta-programme.

The RGO hereby also recommends the following. Make allocation of funds depend on two considerations.

First: whether, in the light of its history, composition and methodology, the research group is capable of performing the research into the desired products. To this end, a group assessment could be carried out to confirm the following points.

a The group is willing for the agenda setting to be influenced in a professional way by the wishes and needs of users. This can lead to public-private-patient-practitioner partnerships (5P's).
b The collaboration between partners is demonstrably good (record of service) and the partners are open to new relevant partners.
c The group demonstrates actual ability to develop new products; not stopping with knowledge development.

Second: whether the product to be developed has sufficient priority in the view of the users. A product assessment should be performed to this end to confirm the following points.

a The survey of users has revealed the need for the product to be developed.
b The product development has priority in view of its significance for the quality, accessibility and affordability of care (weighting in accordance with Criteria 1-4 given in this document).
c The product would be developed too slowly, or not at all, in and by the market (Criterion 5).

The users might sometimes give priority to a product that is beyond the scope of any existing research programme. If so, consideration should be given to creating other funding opportunities within the meta-programme. Subscribing to these new funds should require demonstration that the research really cannot be funded within the existing programmes and that a financial investment is the best solution for eliminating the manifest market failure.

The advisory report entitled *Value for our money. Deciding on public investments in health research* may be of help.[46] It discusses various methods from the medical technology assessment (MTA) that can be used in decisions about the scale and promise of investments in the development of specific products.

Recommendation for the medical products research agenda

> Supplement the research agenda (the twelve clusters) of the 'Innovative Medical Products' meta-programme with the findings of the surveys and prioritisation that have emerged in formulating this advisory report.

In the context of this recommendation it should be noted the survey only covered a limited range of disease areas. Cancer, for instance, was not included. And although public health and prevention were mentioned by the government in the role of pull party, this domain is still inadequately represented in terms of specific products.

In view of the very heterogeneous nature of the products mentioned, the Committee resolved to produce a more generally applicable agenda by clustering specific products. This process led to the following agenda of clustered medical products.

A Regenerative medicine
For example: biological artificial kidney, skin regeneration, gene therapy for orphan diseases

B Therapy based on individual characteristics
For example: medication tailored to age, gender, blood values, genetics, etc.

C New medicinal products and devices targeting the effects of disorders
For example: products to treat fatigue, pain and itching

D Improved versions of existing medication
Mainly aimed at reducing side effects, but also at increased effectiveness

E New medicinal products and devices targeting the disorder
For example: anti-dementia drugs, products to enhance insulin sensitivity

F Early, accurate diagnosis involving less discomfort
For example: replacing endoscopy, systems for measuring existing and new biomarkers

G Patient toolkit to enhance self-management and self-reliance
For example: movement analysis, biofeedback, communication tools

H Improvement and expansion of existing therapeutic interventions
For example: an alternative to thrombolysis, types of dialysis involving fewer complications

I Home automation systems for remote care
For example: camera systems, sensor systems, interactive information systems
J Information processing systems and information exchange systems
For example: improved information systems between carers and between carers and patients, e-learning modules.

In the area of public health, the government has a great need for medical products to combat infectious disease. In view of this, the following two additional clusters have been added:

K New products aimed at preventing disease and promoting health.
L Improved resources aimed at preventing and treating infections.

Recommendation concerned with funding

Other parties besides the Minister of Health, Welfare and Sport also have an interest in and would benefit from a programme oriented to providing incentives for product development as set out in this document. Some examples would include the Ministry of Education, Culture and Science, the Ministry of Economic Affairs, Agriculture and Innovation, health funds, patients' organisations, and existing public-private partnerships and the health industry. For instance, the Association of Health Funds (SGF) in its 2010-2014 strategic plan included the development of medical products within specific clusters as a research priority. Mixed funding is in line with the Innovation Platform's report: *Giving for knowing*.[48]

> Convince all stakeholders of the importance of joint funding for the 'Innovative Medical Products' meta-programme.

Recommendation concerned with dialogue

The 'Innovative Medical Products' meta-programme focuses on products that emerged from surveys of users, and the related prioritisation by experts. This pull approach is new, and is an essential supplement to the pressure on product development that is asserted by the research and development field (academia and industry). However, there is also a limitation: users do not always have a

clear view of the revolutions concealed within the laboratories and research departments of push parties. We must be careful not to lose sight of the products that might be generated by such revolutions. With this in mind, regular discussions should be held between users and researchers/developers. This leads to the final recommendation:

> Regular dialogue meetings should be held between ‘pull’ (users) and ‘push’ (researchers and developers) within the ‘Innovative Medical Products’ meta-programme, with the aim of gaining early insights into product development in the longer term.

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Annexes

Annex **A**

The request for advice

Letter of 5 June 2009 (ref. GMT/IB/2931334) from the Minister of Health, Welfare and Sport to the Chairman of the Advisory Committee on Health Research.

One of the subjects in your programme of activities for 2009 is a 'medical products research agenda'*. My request for an advisory report on this subject is as follows. I request you to advise me on a medical products research agenda, indicating:

- which areas of research have the best prospects for successful application, in view of the public duties of the Ministry of Health, Welfare and Sport, the presence in the Netherlands of industrial activity in this field, and the existing excellent research and knowledge infrastructure;
- where, within these areas of research, priority should be given (define focus areas);
- how the government could best give incentives to research on the above focus areas;
- how account should be taken of the international framework, within which important trends are occurring in this field;
- how, and within what form of control, this agenda can on the one hand be kept dynamic and on the other can form the basis for long-term government policy for research and development of medical innovative products.

The following explains my request in greater detail.

* We define medical products as pharmaceuticals, medical devices and biomaterials.

Explanation

The context
The above request builds on, and is intended to augment, previous work in the area of agenda development that gave rise to the policy on priority medicines, and the medical biotechnology research agenda that it supports.
Close coordination between a triangle of ministries (Health, Welfare and Sport; Economic Affairs; and Education, Culture and Science), together with government investment incentives in recent years, has enabled Life Sciences* & Health to grow into a national innovation area. This successful joint approach is also a launchpad for the future.

The questions
Certain aspects must be reviewed in order to handle government policy on the development and innovation of medical products effectively.

- Which areas of research have the best prospects for successful application, in view of the public duties of the Ministry of Health, Welfare and Sport, the presence of industrial activity in this field, and the existing excellent research and knowledge infrastructure;

Over the next few years, as in the past, public funding of R&D by the Ministry of Health, Welfare and Sport and others will require clear justification. A basic principle in this context will be the public interest of the innovations to be developed, and the market situation in which private parties operate. Please give me details of the criteria to be used to this end.

- Where, within these areas of research, priority should be given (define focus areas);

I request you alongside the proposal for the focus areas that I should use, also to give the technical criteria you used as the basis for your proposal.

- The best way for the government to give incentives to research on the focus areas identified as above;

Having defined the focus areas, the government still has various angles from which to provide incentives. A choice must first be made as to the nature of the incentives to be provided. Providing subsidies is only one of the options in the financial incentives category. There are also other categories of incentives, such as management by speech and dialogue with parties.

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* Life Sciences is defined here as an extremely broad field that includes scientific research into medical products.

What options do you see, and what do you recommend in this regard?

It might also be useful to examine the ways in which the collaborative aspects of projects in this area are organised. Besides the form of public-private partnership that has been frequently chosen to date for precompetitive research, there are many other possible forms of partnership, each with their own advantages and disadvantages.*
It is important for both government and those working in the field to have a clear view of these options in order to increase the likelihood of success of the innovation.

- How should be taken account of the national and international framework within which important trends in this field are occurring.

In this request for advice I would ask you to take account of the following (and to state in your advisory report how you did so):

- my Ministry's recently revised '*Maatschappelijke Opgaven Volksgezondheid en Gezondheidszorg* (Public Duties in Public Health and Healthcare)' (March 2009);
- the '*Maatschappelijke Innovatie Agenda Gezondheid* (Social Innovation Agenda for Health)' (June 2008);
- the scientific situation and current developments of (new) (converging) technologies, such as medical biotechnology, including stem cell technology and (bio) nanotechnology;
- the strengths of the Netherlands in R&D, the market situation in which private parties find themselves, and the opportunities for further development and partnership within Europe, in the light of the existing EU research programmes;
- the Royal Netherlands Academy of Arts and Sciences (KNAW) advisory report entitled '*Gezondheidsonderzoek: het investeren waard* (Health research: worthy of investment)' (2007);
- the findings of your study (in 2009) into options for incentives for participation in European biomedical research programmes;
- the conclusions and recommendations given in your advisory report on early Medical Technology Assessment (MTA) to be issued in 2009;
- the existing Ministry of Health, Welfare and Sport research agendas in the area of priority medicines, prevention, the medical biotechnology research agenda** (and the forthcoming WHO report on medical devices);

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* Alongside R&D (knowledge and money) the process of innovation is also important. It had been shown that social innovation (management skills, innovative organisational forms and advanced employment relationships) can be of overriding importance for the success of an innovation.

** The present the Medical Biotechnology Research Agenda is, for the greater part, being executed. Also due to new developments this agenda may not be up-to-date anymore. Therefore, this agenda – being one of the key elements for your advisory report – should be reviewed critically.

- the Netherlands Organisation for Scientific Research (NWO) programme ‘New instruments for healthcare’;
- the long-term visions to be issued this year by the ‘High Profile Group’ of the LSH innovation programme, and the vision due next autumn, LifeSciences 2020, of the Netherlands Genomics Initiative;
- the decision process for the 2008 and 2009 FES rounds;

Please also take note of the relevant passages in the Strategic Research Agenda for nanotechnology issued on 17 October 2008 by the Netherlands Nano Initiative. Finally, I would like you to incorporate recent international analyses, roadmaps and other studies in this area.

- How can this agenda be kept dynamic while, at the same time, forming the basis for long-term government policy on incentives for research and development work on innovative medical products.

The rapid pace of developments in this broad area demand that the research agenda is kept up-to-date. I therefore need a dynamic agenda, which, as it were, bends with new developments. I also need a vision for a long-term policy that will satisfy the need, which is also felt in the field, for consistency and impact.

This request for advice in principle has an extremely broad scope. For practical reasons it may be necessary to delineate this area well within the common definitions of the corresponding kinds of products, in particular with respect to the medical devices part.*

Clearly defined, but well-balanced, choices will have to be made if government funds for incentives for the research and development of medical products are to be utilised as effectively as possible in the next few years. It is of great importance that your advisory report should provide me with insight into how these choices can be made.
I look forward to your recommendations for a pragmatic agenda, that is supported by the relevant parties working in the field, in May 2010.

sgd
the Minister of Health, Welfare and Sport
Dr A. Klink

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* With respect to the medical devices part, a desirable delineation will depend on the findings expected to come from the WHO report referred to above. It is currently unclear to what extent this WHO report will provide a timely and sufficient basis for forming your advisory report. A decision on this point must be made in the course of your advisory process in consultation with my Ministry.

Annex **B**

The Advisory Committee on Health Research (RGO)

- Prof. P.J. van der Maas, *chairperson* (until 1 July 2010)
  Professor Emeritus of Social healthcare, Erasmus Medical Centre, Rotterdam
- Prof. L.J. Gunning-Schepers, *chairperson* (from 1 September 2010)
  President of the Health Council of the Netherlands, The Hague
- Prof. W.J.J. Assendelft
  Professor of General Practice, Leiden University Medical Centre
- Prof. J.M. Bensing, *deputy chairperson*
  Professor of Health Psychology, University Medical Centre, Utrecht
- Dr A. Boer
  Member of the Board of the Healthcare Insurance Board (CVZ), Diemen
- Prof. J.M.W. Hazes
  Professor of Rheumatology, Erasmus Medical Centre, Rotterdam
- Dr J.W. Hofstraat
  Vice President, Philips Research, Eindhoven
- M.W. Horning, *observer*
  AgentschapNL, Ministry of Economic Affairs, Agriculture and Innovation, The Hague
- Prof. J. Kievit
  Professor of Medical Decision-making, Leiden University Medical Centre
- Prof. P.L. Meurs, *advisor*
  Chairperson of the Netherlands Organisation for Health Research and Development (ZonMw), The Hague

- Dr R. van Olden
  Medical Director, GlaxoSmithKline, Zeist
- Prof. J.J. Polder
  Endowed Professor of Economic Aspects of Health and Care, Tilburg University / Centre for Public Health Future Projections, National Institute of Public Health and Environmental Protection (RIVM), Bilthoven
- Dr J.W.A. Ridder-Numan, *observer*
  Directorate of Research and Science Policy, Ministry of Education, Culture and Science, The Hague
- Prof. S.A. Reijneveld
  Professor of Social Medicine, University Medical Centre Groningen
- H.J. Smid, *advisor*
  Director of the Netherlands Organisation for Health Research and Development (ZonMw), The Hague
- Prof. H.A. Smit
  Professor of Public Health, Julius Centre for Health Studies and Primary Care, University Medical Centre, Utrecht
- Dr C. Smit
  Patients and consumers representative, Hoofddorp
- Prof. A.E.M. Speckens
  Professor of Psychiatry, Radboud University Nijmegen Medical Centre, Nijmegen
- Prof. M.J. Trappenburg
  Endowed Professor of Sociopolitical Aspects of the Welfare State, University of Amsterdam
- Prof. E.G.E. de Vries, *advisor*
  Chairperson of the Council for Medical Sciences (RMW), Amsterdam
- Prof. R. Vos
  Professor of Health Ethics and Philosophy, Maastricht University
- Dr C.M. Vos, *observer*
  Directorate of Macroeconomic Issues and Employment Conditions Policy, Ministry of Health, Welfare and Sport, The Hague
- Dr J.N.D. de Neeling, *scientific secretary*
  Health Council of the Netherlands, The Hague

Annex **C**

The Committee

- Prof. G.H. Blijham, *chairperson*
  Professor of Internal Medicine, University Medical Centre Utrecht
- Prof. W.E. Fibbe
  Professor of Haematology (stem cell biology), Leiden University Medical Centre
- Dr J.W. Hofstraat, *advisor*
  Vice President, Philips Research, Eindhoven
- M.W. Horning, *observer*
  AgentschapNL, Ministry of Economic Affairs, Agriculture and Innovation, The Hague
- Prof. M.J. IJzerman
  Professor of Clinical Epidemiology and Health Technology Assessment, University of Twente, Enschede
- Prof. B. Löwenberg
  Professor of Haematology, Erasmus Medical Centre, Rotterdam
- Prof. P.J. van der Maas
  Professor Emeritus of Social Healthcare, Erasmus Medical Centre, Rotterdam
- Dr R. van Olden, *advisor*
  Medical Director, GlaxoSmithKline, Zeist

- Dr C. Oosterwijk
  Director Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (VSOP), Soest
- Prof. J.H.C. Reiber, *advisor*
  Chairman of the Theme Committee NWO-IMDI.NL, The Hague / Professor of Medical Imaging, Leiden University Medical Centre
- Dr J.W.A. Ridder-Numan, *observer*
  Directorate of Research and Science Policy, Ministry of Education, Culture and Science, The Hague
- J.B. van den Wijngaard, *observer*
  Directorate of Medicines and Medical Technology, Ministry of Health, Welfare and Sport
- S.W. Donk, MSc, *national government trainee*,
  Ministry of Economic Affairs, Agriculture and Innovation, Health Council of the Netherlands (from 1 September 2009 to 1 September 2010), The Hague
- Dr S.H.M. Litjens, *scientific secretary*
  Health Council of the Netherlands, The Hague
- Dr V.W.T. Ruiz van Haperen, *scientific secretary*
  Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **D**

Experts consulted

The academic world

- Prof. A.J. van Balkom, Professor of Evidence-Based Psychiatry, VU University Medical Centre, Amsterdam
- Prof. P.J.E. Bindels, Professor of General Practice, Erasmus Medical Centre Rotterdam
- Prof. J. Dekker, Professor of Paramedical Care, VU University Medical Centre Amsterdam
- Prof. D.A.J.P. Denys, Professor of Psychiatry, Academic Medical Centre Amsterdam
- Prof. J.M.W. Hazes, Professor of Rheumatology, Erasmus Medical Centre Rotterdam
- Prof. P.A.J. Hilbers, Professor of Biomodelling & Bioinformatics, University of Technology, Eindhoven
- Prof. D.W. Hommes, Professor of Gastrointestinal and Liver Diseases, Leiden University Medical Centre, Leiden
- Prof. W.J.G. Hoogendijk, Professor of Biological Psychiatry, VU University Medical Centre Amsterdam
- Prof. J.M.M. Hooymans, Professor of Ophthalmology, University Medical Centre Groningen
- Prof. P.C. Huijgens, Chairman of HOVON
- Prof. L.J. Kappelle, Professor of Neurology, University Medical Centre Utrecht

- Prof. P.J. Koudstaal, Professor of Neurology, Erasmus Medical Centre Rotterdam
- Prof. E.J. Kuipers, Professor of Clinical Gastroenterology, Erasmus Medical Centre Rotterdam
- Prof. G.P.M. Luyten, Professor of Ophthalmology, Leiden University Medical Centre, Leiden
- Prof. B. Prakken, Professor of Paediatrics, University Medical Centre Utrecht
- Prof. P. Scheltens, Professor of Cognitive Neurology Alzheimer Centre, VU University Medical Centre Amsterdam
- Prof. M.J. Schuurmans, Professor of Nursing Studies, University Medical Centre Utrecht
- Prof. M.L. Simoons, Professor of Cardiology, Thorax Centre, Erasmus Medical Centre Rotterdam
- Prof. P. Sonneveld, treasurer of HOVON, Amsterdam
- Prof. A.E.M. Speckens, Professor of Psychiatry, Radboud University Nijmegen Medical Centre, Nijmegen
- Prof. V. Subramaniam, Professor of Nanobiophysics, University of Twente, Enschede
- Prof. F.R.J. Verhey, Professor of Geriatric and Neuropsychiatry, Academic Hospital Maastricht
- Prof. F.L.J. Visseren, Professor of Vascular Medicine, Academic Medical Centre Amsterdam
- Prof. M. de Visser, Professor of Neurology, Amsterdam University Medical Centre, Amsterdam
- Prof. L.J. van Vliet, Professor of Image Analysis, TU Delft

Industry and public-private top institutes

- Prof. A.F. Cohen, Director of the Centre for Human Drug Research (CHDR), Leiden
- Dr W.N.G.M. de Laat, Director of TIPharma, Leiden
- Prof. P.R. Luijten, CSO Center for Translational Molecular Medicine (CTMM), Eindhoven
- Prof. H.J. Out, Deputy Chairman of Clinical Research MSD (formerly Organon), Oss
- H.G.C.P. Schikan, CEO Prosensa, Leiden
- H.E. Viëtor, CEO Skyline Diagnostics, Rotterdam

- Working visit to Philips Research, Eindhoven:
  - S. Dijkstra, Clinical Decision Support
  - P. van Deursen, Home Healthcare
  - W. Crooijmans, Image Guided Intervention and Therapy
  - Dr G. Friesen, Government Relations Office

Patients and care providers

The RGO engaged the Athena Institute to consult patients and care providers (see attached background report[1]). In total the Athena Institute consulted 169 patients and 64 care providers.

For the Duchenne Parent Project case Dr E. Vroom, chairperson of DPP Nederland, was consulted.

Funding bodies

- Dr G. Boerrigter, Chairman of the SGF Research Committee and Head of the KWF Kankerbestrijding Research Programme based in Amsterdam
- Dr J.M. Boomker, Implantable Artificial Kidney programme manager, Dutch Kidney Foundation, Bussum
- R. Gorter, Chairman of SGF and Director of Fonds Psychische Gezondheid, Amersfoort
- Dr A.G.J.M. Hanselaar, Deputy Chairman of SGF and General Director of KWF Kankerbestrijding, Amsterdam
- T. Oostrom, Deputy Director of the Dutch Kidney Foundation (general director as of 1 August 2010), Bussum
- Dr C. de Visser, Director of Netherlands Organisation for Scientific Research (NWO), The Hague

Government organisations

- Ministry of Health, Welfare and Sport: Directorate of Medicines and Medical Technology
  - Dr F.J. Flier
  - J.A.C. van Ginneken
  - B. Wijnberg
  - J.B. van den Wijngaard
- Ministry of Health, Welfare and Sport: Directorate of Curative Care
  - Dr R.W. Segaar

- Ministry of Health, Welfare and Sport: Directorate of Public Health
  - Dr P.J. van Dalen
  - L.J. van der Heiden
  - Dr G.J. Olthof
- Ministry of Health, Welfare and Sport: Directorate of Chronic Care
  - I.S. Kishna
- Ministry of Health, Welfare and Sport: Directorate of Macroeconomic Issues and Employment Conditions Policy
  - J. de Groot, MSc.
  - Dr C.M. Vos
- Netherlands Bureau for Economic Policy Analysis
  - A.S. Verrips, FES projects assessment project leader

Annex **E**

Reflection meeting participants

Some participants have multiple roles in daily life. For instance, many researchers belong not only to the push, but also to the pull (as care provider) and some researchers are also RGO members. The participants are listed below in the capacity in which they were invited to participate.

Patients and care providers (pull)

- Mr W.F. (Wim) van Baarle
  CVA Vereniging Samen Verder, Castricum
- Ms W. (Wiena) Bakker
  Nederlandse Leverpatiënten Vereniging, Amersfoort
- Mr P. (Pim) de Boer
  Asthma Fund, Leusden
- Ms J. (Jacquelien) Dros
  Academic Medical Centre, Department of General Practice, Amsterdam
- Ms D.T. (Tine) Greidanus
  Stichting Viziris, Utrecht
- Mr G. (Geert) Joosten
  Stichting Viziris, Utrecht
- Mr K. (Klaas) Kok
  EPP (erythropoietic protoporphyria) Vereniging, Maassluis
- Ms D. (Dorothee) Laan
  Asthma Fund, Leusden

- Ms T. (Tineke) Markus
  Crohn en Colitis Ulcerosa Vereniging Nederland, Woerden
- Ms J. (Jacqueline) Moelands
  Landelijke Federatie Belangenverenigingen Onderling Sterk, Utrecht
- Ms J.J. (Jacquelien) Noordhoek
  Nederlandse Cystic Fibrosis Stichting, Baarn
- Ms G.W.L. (Germieke) Quist-Anholts
  nurse, Hogeschool Leiden
- Ms F. (Fien) Stellingwerff-Beintema
  Irritable bowel syndrome interest group, Voorhout
- Ms H. (Hanne) Velthuis
  Reumapatiëntenbond, Amersfoort
- Ms J.E. (Hanneke) Voorneveld
  Maasstad Hospital/ V&VN (Nurses and primary care providers association), Oosterwijk
- Ms H. (Hendriët) Wanders
  Vereniging van Mensen met Brandwonden, Beverwijk
- Mr W. (William) Westveer
  Landelijke Federatie Belangenverenigingen Onderling Sterk, Utrecht
- Ms A.C. (Anna) Zentveld
  Vereniging van Mensen met Brandwonden, Beverwijk

Academic world and industry (push)

- Mr D.A.J.P. (Damiaan) Denys
  Academic Medical Centre, Department of Psychiatry, Amsterdam
- Mr R.E. (Robert) Geertsma
  National Institute of Public Health and Environmental Protection, Bilthoven
- Mr J.G. (Johan) Hanstede
  BioFarmind, The Hague
- Ms J.M.W. (Mieke) Hazes
  Erasmus Medical Centre, Department of Rheumatology, Rotterdam
- Mr W.J.G. (Witte) Hoogendijk
  VU University Medical Centre / Mental healthcare inGeest, Amsterdam
- Mr P.J. (Peter) Koudstaal
  Erasmus Medical Centre, Department of Neurology, Rotterdam
- Ms N. (Nellie) Kraaijeveld
  Nefarma, The Hague

- Mr E.J. (Ernst) Kuipers
  Department of Gastrointestinal and Liver Diseases, Erasmus Medical Centre, Rotterdam
- Mr P.R. (Peter) Luijten
  Center for Translational Molecular Medicine, Eindhoven
- Mr G.P.M. (Gré) Luyten
  Leiden University Medical Centre, Department of Ophthalmology, Leiden
- Ms M.J. (Marieke) Schuurmans
  University Medical Centre Utrecht, Nursing Studies, Utrecht
- Mr H. (Henk) Viëtor
  Skyline Diagnostics B.V., Rotterdam
- Mr F.L.J. (Frank) Visseren
  Department of Vascular Medicine, University Medical Centre, Utrecht

Government organisations

- Mr G. (Gerrit) van Ark
  Netherlands Organisation for Scientific Research (NWO), The Hague
- Mr F.J. (Frank) Flier
  Ministry of Health, Welfare and Sport, The Hague
- Ms J.W.A. (Jeannette) Ridder-Numan
  Ministry of Education, Culture and Science, The Hague
- Mr J.H. (Hans) van der Veen
  Stichting Toekomstbeeld der Techniek, The Hague
- Mr C.M. (Cees) Vos
  Ministry of Health, Welfare and Sport, The Hague
- Mr G. (Geert) Wassink
  Netherlands Organisation for Health Research and Development (ZonMw), The Hague

Organisation and support

- Mr G.H. (Geert) Blijham
  Committee chairperson
- Ms J.E.W. (Jacqueline) Broerse
  Athena Institute, VU University Amsterdam, Amsterdam
- Ms S.W. (Sabine) Donk
  Health Council of the Netherlands, The Hague
- Ms J. (Janneke) Elberse
  Athena Institute, VU University Amsterdam, Amsterdam

- Mr J.W. (Hans) Hofstraat
  Committee advisor
- Ms J.W. (Janine) van de Kraats
  Athena Institute, VU University Amsterdam, Amsterdam
- Ms S.H.M. (Sandy) Litjens
  Health Council of the Netherlands, The Hague
- Mr P.J. (Paul) van der Maas
  Committee member, also former RGO chairperson
- Mr J.N.D. (Nico) de Neeling
  Health Council of the Netherlands, The Hague
- Mr R.W. (Rudolf) van Olden
  Committee advisor
- Mr C. (Cor) Oosterwijk
  Committee member
- Ms C.A.C.M. (Carina) Pittens
  Athena Institute, VU University Amsterdam, Amsterdam
- Mr J.H.C. (Hans) Reiber
  Committee advisor
- Ms V.W.T. (Veronique) Ruiz van Haperen
  Health Council of the Netherlands, The Hague
- Ms G.A.J. (Gwen) Soete
  Health Council of the Netherlands, The Hague
- Ms M.H.F. (Marjolein) van Wijk
  Athena Institute, VU University Amsterdam, Amsterdam

Annex **F**

Definitions of terms

Biomaterial

A synthetic, natural or modified material, designed for implantation in (or interaction with) living systems. Biomaterials are used in the context of regenerative medicine.

Market failure

Market failure means that there is a mismatch between supply and demand: there is a need for medical products, but they are not materializing. The cause must be sought in poor performance of one or more key processes in the innovation system.

Medicine

A simple substance or compound with therapeutic or prophylactic properties with respect to human diseases, or that can be used with or administered to patients either to rectify, improve, or alter physiological functions by producing a pharmacological, immunological or metabolic effect, or to make a medical diagnosis.

Medical device

Therapeutic, diagnostic or supporting devices. This advisory report refers to ‘devices for diagnosis and care’.

Pull

Users of knowledge and products of scientific research.

Push

Parties that generate knowledge and products by means of scientific research.

Regenerative medicine

A branch of medicine concerned with the functional recovery of damaged tissues and organs through the use of tissues and cells, or the properties thereof.

Translational research

Translational research is a phase in the knowledge chain that comprises all the steps from the identification of diagnostic leads, prevention and therapy (in patients or patient material), to early clinical application in practice. Questions may come from either from those in the field of clinical practice or from laboratory workers.

Annex **G**

‘What’ question method

G1 Choice of fifteen disease areas

The list of fifteen disease areas was arrived at on the basis of four criteria:

- the burden of disease in the Netherlands (source: National Institute of Public Health and Environmental Protection (RIVM))
- the costs of the disorder in the Netherlands (source: National Institute of Public Health and Environmental Protection (RIVM))
- the expert opinion of the appointed committee members
- the existence of research agendas from the patient’s perspective.

Research agendas from the patient’s perspective had already been drawn up for seven disorders: respiratory disorders; burns; diabetes; paraplegia; kidney disorders; muscle disorders and intellectual disability. Paraplegia was dropped because the agenda included only sociopsychological research and had no reference points for medical products.

Based on the first three criteria, the Committee selected ten disorders for which no research agendas yet existed. In order of urgency they are: cardiovascular disorders; locomotor disorders; dementia; depression; rare disorders; stroke (CVA); gastrointestinal and liver disorders; nerve disorders; anxiety disorders; and cancer. The importance of this sequence was for the following reason. In order to preserve the method’s scientific robustness, an estimate was made after each focus group of whether the finding was

representative for the disease area concerned. If not, a second focus group was held for the disease area. The limited time and funds available meant that disease areas at the bottom of the list might have to be abandoned. This happened in one case, in that no survey was possible for the cancer disease area. There were two reasons for this major and serious disease to be put at the bottom of the list. First, much research has already been performed in this area, and second, it is such a heterogeneous disease area that it is almost impossible to gather a relative homogeneous patient group for it in the focus group. For the same reason, nerve disorders were restricted to visual impairments.

The fifteen disorders that the Committee ultimately selected are shown in Table 2 in Section 3.2.

G2 The assignment of product priorities through multicriteria analysis

AHP method

In prioritising medical products, multiple criteria are weighed and the performance of each of the products is assessed in accordance with a given criterion. The prioritisation can also be substantiated by means of multicriteria decision analysis. The Analytic Hierarchy Process (AHP) is a technique for multicriteria decision analysis in support of complex decisions.[49] The AHP involves a hierarchical decision tree (see Figure 10). An appraisal is then performed, involving multiple criteria and products. The relevant factors for the allocation of priority are the criteria presented in Section 3.2.3. A value is assigned, indicating the degree to which each medical product meets the criteria in question.

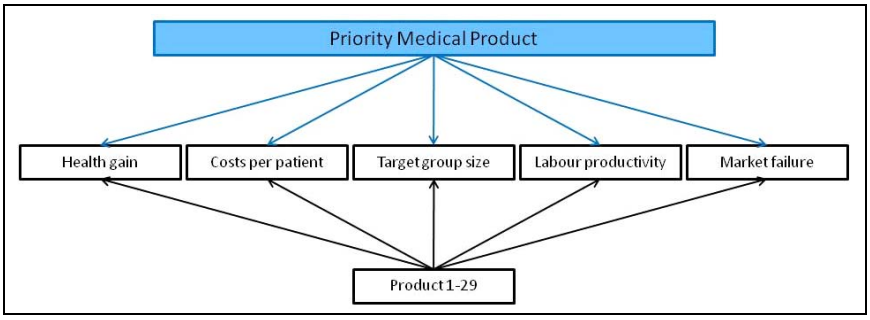

Figure 10 The decision structure.

An advantage of the AHP method over other techniques is that the analysis and appraisal can be carried out in a group. The scores are collected and visually presented to the entire group. The group members can then adjust their scores in the light of the ensuing discussion. This approach guarantees that all the expertise available is shared. At the same time, the AHP method provides scope for differences of opinion. It is not a requirement that the assessors should reach agreement. The ultimate finding for a medical product depends on the value given for each criterion and the relative values of the criteria.

Weighing the five main criteria

The relative values of the criteria were established based on ten paired comparisons. An example of a paired comparison ($A_{1,2}$ in Table 10) is shown in Figure 11.

All paired comparisons ($A_{1,2}$ to $A_{4,5}$) are shown in Table 10.

Table 10 Ten paired comparisons, on which basis the relative values of the criteria were determined. For the criteria 1 – 5, see Section 3.2.3.

$A_{criteria}$	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5
Criterion 1		$A_{1,2}$	$A_{1,3}$	$A_{1,4}$	$A_{1,5}$
Criterion 2			$A_{2,3}$	$A_{2,4}$	$A_{2,5}$
Criterion 3				$A_{3,4}$	$A_{3,5}$
Criterion 4					$A_{4,5}$
Criterion 5					

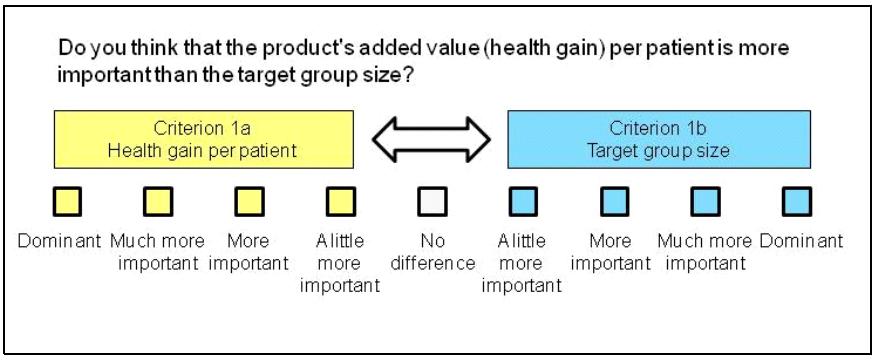

Figure 11 Example of a paired comparison ($A_{1,2}$ from Table 10). All paired comparisons in Table 10 were performed in this way.

Inconsistency ratios

Ten paired comparisons were needed to assign weights to five main criteria. Consequently it is possible for an inconsistency to arise in the assessment. If Criterion 1 is more important than 2, and Criterion 2 is more important than 3, then Criterion 1 must also be more important than 3 in order to be consistent. As a rule of thumb, inconsistency scores of 0.1 are considered acceptable. If the answers to the questions reveal that a committee member was inconsistent, the scoring was repeated. Ultimately all committee members had consistent scores.

The paired comparisons of all committee members led jointly to the relative values in Table 3 in Section 3.2.

Evaluation of the medical products per criterion

The Committee spent a full day assessing the two most specific medical products of the top three products in each disease area (see Figure 12). Paired comparison of the medical products was impossible in view of the large number of products to be assessed. Accordingly, the medical products were assigned an absolute value for each criterion.

The value for Criterion 2 (target group size) was determined from available prevalence data (sources: National Institute of Public Health and Environmental Protection (RIVM); Statistics Netherlands; websites of patients' organisations or health funds; and the expert opinion of the experts consulted). The prevalence data used by the Committee are given in Table 11.

All product scores (-9, -5, 1, 5 and 9) were then converted into a weight on a linear scale with extreme values 0.1 and 0.9. For Criterion 2 (target group size, see Table 11), the prevalence figures were converted to a scale between 0.1 and 0.9. The lowest prevalence figure (0.04%) was then assigned a value of 0.1, and the highest prevalence figure (15%) a value of 0.9.

The final value for product priority is obtained by multiplying the weight of the criterion by the score of the product on that criterion. (see Table 3 in Chapter 3). This means that for Criterion 1 (health gain) the scores are between 0.039 and 0.351; for Criterion 2 (target group size) between 0.012 and 0.108; for Criterion 3 (costs) between 0.017 and 0.153; for Criterion 4 (labour saving) between 0.01 and 0.09 and for Criterion 5 (market failure) between 0.022 and 0.198. Criterion 6 (knowledge base) was restricted to the determination of a product score, and no weight was assigned to this criterion. The scores for this criterion therefore varied between 0.1 and 0.9.

Criterion 1: The added value of the product for the patient (health gain)

AHP score	9	5	1	5	9	
Low priority	Little added value	Reasonable added value	Fairly large added value	Large added value	Very large added value	High priority

Criterion 3: Application of the medical product entails additional costs or additional savings *per patient*

AHP score	9	5	1	5	9	
Low priority	Very many additional costs	Fairly many additional costs	Hardly any additional costs	Savings	Major savings	High priority

Criterion 4: Application of the medical product leads to a change in the patient's professional care need.

AHP score	9	5	1	5	9	
Low priority	Much greater professional care need	Greater professional care need	No influence on professional care need	Less professional care need	Much less professional care need	High priority

Criterion 5: There are identifiable reasons why the product would probably not be developed in the market unaided (i.e. a market failure situation).

AHP score	9	1	9	
Low priority	None or hardly any signs of market failure	Some signs of market failure	Clear signs of market failure	High priority

Criterion 6: There is a sound knowledge base in the Netherlands for bringing the innovation to fruition.

AHP score	9	5	1	5	9	
Low priority	Poor knowledge base	Fairly poor knowledge base	Reasonable knowledge base	Good knowledge base	Excellent knowledge base	High priority

Figure 12 Score sheet for five of the six criteria.

Table 11 Prevalence figures used for Criterion 2 (target group size).

Disease area	Medical products	Target group size
Locomotor system	Gait analysis	15%
	Cartilage and bone regeneration	11%
Respiratory difficulties	Anti-fatigue agent	7.4%
Anxiety disorders	Biofeedback	6.5%
	Medication to counter fluctuations in sex hormone levels	3.9%
Burns	Anti-itching agent for scars Tissue regeneration	0.35%
		0.35%
Cardiovascular	Reduction of statin side effects Myocardial stem	4.6%
	cell therapy	2.3%
CVA	Neuralgia treatment	0.23%
	Alternative for immediate postinfarct thrombolysis	1.6%
Dementia	Devices to counter memory impairment	1.3%
	Dementia inhibitors	1.3%
Depression	Better antidepressants	3.3%
	Diagnosis based on biomarkers	3.3%
Diabetes	Combined sensor and pump for blood glucose regulation	3.9%
	Agent for increasing the sensitivity of body tissues to insulin (type II)	3.5%
Gastrointestinal Liver	Alternative for endoscopy	4.3%
	Active ingredients in food	4.3%
Kidney diseases	Implantable biological artificial kidney	0.04%
	Less harmful forms of dialysis	
		0.04%
Muscle diseases	Pain control	1.2%
	Brain Computer Interfaces	1.2%
Intellectual disability	Communication devices Neonatal screening	0.6%
		0.6%
Visual impairment	Navigation systems	1.8%
	Early and correct diagnosis	1.8%
Rare disorders	Gene therapy	0.05%
Disease-transcending	Individualised medication	3%

Experience during the appraisal

The opportunity to harness one another's knowledge and expertise during the assessment process was much appreciated by the committee members.

It is useful to classify the 'individualised medication' product as disease-transcending. This is because the product in question is relevant to all disease areas, and has actually been cited in connection with many of these areas. In practice, however, it is often difficult for the assessors to make disease-

transcending judgements. This is because the health gains, costs/savings, changes in the level of professional care required, market failure, and existing knowledge base all depend on the disease area for which the product is intended. It is also relevant to ask which value should be assigned for target group size. On this point, the Committee opted for an average value for the disease areas in question (see Table 11).

G3 Reflection meeting: interactive link between pull and push

The Committee held a reflection meeting to create a dialogue that would allow the representatives of push and pull to reflect on the content of the research agenda, on its creation process, and on implementation strategies. This session generated feedback on the process, on content and on implementation. Its secondary objective was to set up a dialogue within which the push and pull could interact with each other. In all, there were thirty-seven participants (see Annex E), in addition to the members of the Committee and employees of the Health Council (GR) and the Athena Institute.

The Committee divided the participants into three smaller discussion groups, which were as mixed as possible. The questions below, clustered into three themes, were set in parallel sessions.

Method

- Were the right parties involved (pull and push)?
- Were the parties involved in an effective way?
- Was the input given by the various parties appraised in an accurate way?
- Was the process sufficiently transparent for the participants?

Findings

- Was the input from both pull and push sufficiently identifiable in the findings?
- Were any essential matters overlooked?
- Were any medical products wrongly included in the agenda?
- What were the similarities and differences between the input of pull and push; what were the underlying reasons, and how should the RGO respond?

Implementation

- How could the Ministry of Health, Welfare and Sport provide incentives for research into and development of the medical products?

- What parties should have a part in research and the development, and how?
- What factors obstruct development?
- What factors promote development?

After a plenary feedback session there was an open discussion on all three of the above themes.

Annex **H**

Relationship of the research agenda with previously published reports and expert opinions

This research agenda is not an isolated case. It is embedded in a context of other activities and reports concerned with research into medical products, or with their development. In his request for advice, the Minister expressly asked the RGO to take account of this national (and international) context. The national and international context was a constant factor during the drafting of this advisory report. This annex sets down the details of how the research agenda relates to other activities and reports, including those mentioned by the Minister.

International context

The familiar issues in the care sector are relevant not only in the Netherlands but worldwide, or at least in Western countries. An ageing population, rising costs, a shortage of workers, quality and safety, are among the key concepts involved.

The World Health Organisation (WHO) has responsibility under the United Nations for matters such as the definition of research agendas in the health field. In recent years the WHO has issued two agendas in the area of medical products: Priority Medicines (2004) and Priority Medical Devices (2010).[21,23] As the social perspective was paramount, these agendas focus substantially on innovations for developing countries.

With respect to medical devices (referred to in this document as medical devices for diagnosis and care) the WHO observes that there is already an abundance of products. It therefore urges against an exclusive focus on efforts

for innovation. Instead it favours the selection and effective application of medical devices for which an actual need exists. The WHO has used this approach for fifteen disease areas with the highest global burden of disease. This involved a systematic analysis to determine which medical devices are needed, in accordance with the guidelines for tackling the disease concerned. There was also an attempt to identify any mismatch with current practice.

This is dealt with more specifically in the present RGO advisory report by asking patients and care providers to identify perceived gaps in the range of available medical products. This method is also in keeping with the appeal made by the WHO, that medical products be selected for which a real need exists among users. Also, that these should be developed in a way that will enable end-users to utilise them effectively and efficiently. In addition, the prioritisation method developed by the RGO helps to rationalise the available choices. Finally, the present research agenda adds details that are consistent with needs observed by the WHO, to the extent that they apply in Western countries.

Science and innovation are activities that span international frontiers. Accordingly, researchers and companies are constantly on the lookout for international joint venture partners who can add value to their own product research and development.

With this in mind, it makes sense to place the research agenda in an international context, both in terms of content and implementation. The agenda's content will not exclusively reflect the need of the Dutch pull, but rather the pull in most Western countries. For this reason it would be appropriate to distribute this agenda internationally, e.g. within the EU.

By examining the existing knowledge base, this advisory report answers the implementation question of 'What makes the Netherlands the right place for research and development'. If the knowledge base is satisfactory, the Netherlands can play a significant part in that area, possibly in collaboration with excellent international partners. If the knowledge base is unsatisfactory, there are two possible variants. Where other countries have a satisfactory knowledge base, the Netherlands should place research and innovation on the international agenda, e.g. through the European Framework Programme. If the global knowledge base is deficient in certain areas, then the Netherlands can embark on development of the knowledge and the knowledge infrastructure. This would mean assuming a leading international role, which will attract international partners.

The policy context in the Netherlands

The policy context arises from the social context. The Ministry of Health, Welfare and Sport has formulated public duties that respond to social issues such as labour shortages. In brief, the Ministry of Health, Welfare and Sport's public duties are aimed at enabling people to live longer, in good health, with high quality. affordable, , patient-oriented care, and with an adequately staffed health service.[3]

In the context of its public duties, the government attaches importance to encouraging innovation. For this reason, the government has drawn up several knowledge and innovation agendas. For instance, there is the Ministry of Health, Welfare and Sport document on innovation in prevention and care and the *Maatschappelijke InnovatieAgenda Gezondheid* (MIA-G).[50,51] Government knowledge and innovation agendas of this kind provide a framework and facilitate the creation of conditions. This is of use in identifying the right direction, and ways in which the government can help to shape the right conditions for innovation by those in the field.

The patient-oriented research agenda presented in this RGO advisory report is a refinement of these government agendas. The criteria used in this document for prioritising medical products are compatible with the government's public duties of health gain, costs and labour productivity. The present research is more specific in terms of content, it also provides more specific handles for creating conditions and implementing the agenda.

Other RGO advisory reports also address the government's role in setting conditions, such as *Paying upfront*, on matching European research grants; 'Grinding links', on obstacles in the Dutch innovation infrastructure; and the advisory report about early MTA.[2,12,46] The tools recommended in the advisory report about early MTA would be excellently usable in the 'Innovative Medical Products' meta-programme proposed in this document. The rather older RGO advisory reports entitled *Infectious diseases knowledge infrastructure* and *Pharmaceutical care knowledge infrastructure* certainly also have recommendations that are still current, and can help improve conditions for the successful implementation of the meta-programme.[52,53]

The scientific context

The decision was taken to base the present RGO advisory report on medical products rather than on scientific areas. In general, the Netherlands has a good

track record in health research. This is evident from Chapter 2 of this document, as well as from various other reports and research agendas and strategies that have been published.[4,5,28,37,54,55] Examples of specific scientific areas in which the Netherlands is strong also emerged from the various interviews held with the push while formulating this advisory report. These include nanotechnology, imaging, stem cell biology, and rheumatology (N.B. this is definitely not an exhaustive list).

Excellent national interdisciplinary research will generate numerous medical products in the Netherlands. The fact that we have many good researchers, working in various disciplines, and within a small area works to our advantage. If specific sub-disciplines that are vital to the research and development effort are not available in sufficient quantity in the Netherlands, Dutch researchers will be able to find the top-quality researchers needed in other countries. However, this is conditional on an increased emphasis on the creation of interdisciplinary partnerships.

However there are also areas with a less substantial scientific basis, such as paediatrics. Studies involving children are complex both ethically and medically. This is a global problem. The RGO mapped out this problem in the advisory report entitled *Diseases in childhood*.[56] The task of filling this internationally perceived knowledge gap may create opportunities for the Netherlands.

The market context

In order to set an agenda, the present advisory report has primarily adopted the same perspective as the Ministry of Health, Welfare and Sport. Market considerations may also be involved in product prioritisation, e.g. those based on the Ministry of Economic Affairs, Agriculture and Innovation's operational considerations. The government is not always required to make its own choices, in this regard. Instead, it can use the proposed process of subscription to delegate part of this to the public-private joint venture partners themselves. The development of an international agenda can also serve to activate the international market.

Annex I

Cases for the ‘how’ question

Case 1: HOVON

Strengths

- One of HOVON’s strengths is the strong organisation of the profession, both academic and peripheral. This came about because of its focus on trials (evidence-based care). Because participation is open to all care institutions, the output of trials can be distributed and implemented efficiently. Accordingly, there is no need for the compulsive external control that is intended to improve the quality of care (but is often ineffective in this regard).
- HOVON performs well and has an excellent reputation. Having been set up through intrinsic motivation and with its own funds, HOVON has acquired a sturdy foundation. It is therefore unlikely to collapse like a house of cards at the slightest setback. HOVON enjoys international esteem. It has proven itself able to survive without external funding.
- HOVON covers a substantial part of the innovation cycle. HOVON’s core business is the development and performance of trials; depending on the type of trial to be performed: the development and testing phase of the innovation cycle. However, as HOVON has continued to grow, other phases of the innovation cycle have been added, such as fundamental research and development into valid diagnostic tests, national distribution and

implementation of new knowledge and products, and national monitoring of the quality of care, from which new questions may arise.
- HOVON has good relations with patient representatives. A fruitful partnership has arisen by focusing on the common interests of HOVON and patients' organisations. This in turn presents opportunities for further partnership in the innovation process.

Weaknesses

- HOVON depends strongly on industry for the funding of trials, but would prefer to be less dependent on this party. This is not strange from HOVON's perspective, in that it has found in practice that industry's interests and those of the profession are not always the same. They have found only limited common ground.
- As yet patients have no say in setting up HOVON's research agenda. It is hard to define a role for patients in setting up research agendas and research protocols. Furthermore, some of the patient representatives lack the considerable expertise required by such a role.

Opportunities

- HOVON would utilise additional rudimentary funding very efficiently. One strength of this demonstrably successful organisation is that it was set up through intrinsic motivation and by means of its own funds. Additional funding would enable HOVON to apply its strengths, even more effectively than it does now, for the benefit of a specific group of patients within the Dutch healthcare system.

Threats

- If, for whatever reason, industry should decide to withdraw support from HOVON, there would be unfavourable repercussions for HOVON's standing and influence. This, in turn, would impact the improvement of care for patients with malignant haematological disorders.

Case 2: Duchenne Parent Project (DPP)

Strengths

- Perhaps DPP's greatest strength is the enormous personal drive of the participating parents.
- DPP has succeeded in creating a lean and mean organisation, free of obligations to pay salaries, rent and similar expenses. This enables the bulk

of the funds obtained to be utilised for research. This organisational form is probably only possible because of the great commitment of its members (see first point).
- DPP doesn't care much about the established order. The organisation is unimpressed with the sometimes paternalistic attitude and sluggish bureaucracy of various parties; if the people who 'make' DPP are told that something is impossible, they will work even harder to achieve it.
- DPP makes great demands on research projects that seek to be eligible for funding.
- DPP will sit around the table with anyone who may be able to contribute to its objective, and has good contacts within the academic world and industry.

Weaknesses

- DPP funds research that aims to cure Duchenne. However, patients may also benefit from other research, e.g. into devices for greatly improving their quality of life. However, DPP's funds are insufficient for it to support research in this area too.
- The organisation's small scale is its strength, but it is also a threat to its continuity. If the current initiators were to withdraw, its continued existence in the same form and with the same quality requirements could no longer be taken for granted.

Opportunities

- DPP can serve as an effective role model for user involvement, one that is oriented towards quality, rather than sympathy.
- Medical-ethical legislation in the Netherlands is badly out of step with the surrounding countries. This means that Dutch patients are often excluded from participation in clinical studies. The Committee for Medical-Scientific Research Involving Minors (also known as the Doek Committee) recently advised in favour of legislative amendment. An amendment would offer major opportunities for Dutch children with Duchenne, by making it easier for them to participate in clinical research that could help save their lives.

Threats

- The nature of the disorder means there is little time for research. There is constant pressure to come up with a treatment in the short term. Patient-bound research, certainly with children, is difficult and time-consuming, not least because of the lengthy ethical review procedures involved (in the Netherlands, at any rate).

- Duchenne is a rare disorder. There is a risk that the reimbursement of medication will continue to be administered through the regulation for orphan medicinal products. This route is not necessarily advantageous, in that it allows a single company to retain a monopoly for a longer period of time. This will delay the appearance of generics on the market and the prospect of less expensive medication.

Case 3: Implantable artificial kidney (Dutch Kidney Foundation)

Strengths

- The Dutch Kidney Foundation occupies a strong position between the push and pull, and is therefore in a position to build bridges. On the one hand the Dutch Kidney Foundation has access to the network of push parties (research and industry) and, as a funding body, can even be seen as a push party itself. On the other hand, the Dutch Kidney Foundation's focus is on the patient's perspective, and it is well aware of the needs of kidney patients. In this respect, it can be seen as a pull party. This situation would appear to be an ideal starting point.
- Idealism (the best possible treatment for kidney patients) and enthusiasm contribute to its success in attracting other parties.
- As a health fund, the Dutch Kidney Foundation has funds of its own that it can use to finance pilot projects in support of a proof-of-concept.
- Consortia were formed in a period when little or no money was available for achieving the ambitions. Furthermore, the Dutch Kidney Foundation has formulated a joint interest to which all stakeholders have given their commitment. These consortia are unlikely to quickly or spontaneously collapse when the BMM funding ends.
- The interim reports required by BioMedical Material Programme (BMM) are of use in monitoring the project's progress (biological artificial kidney). In this way, it is possible to determine whether milestones have been achieved, and whether intervention is necessary.
- The Dutch Kidney Foundation has succeeded in creating enthusiasm in industry. It is well aware that a sound business case is the only way to retain this interest.
- The implantable artificial kidney is expected to have a sound business case. This is because it may ultimately improve the quality of life for dialysis patients. There will be greater self-management, while treatment costs and other expenses will decline (in particular through lower personnel costs and

costs for dialysis centres). This last point may be relevant within the framework of the increasing cost of care.

Weaknesses

- Internal funds are insufficient to generate revolutionary innovations, such as the implantable artificial kidney. There is, therefore, a degree of dependence on the 'chance' availability of funds, such as a FES programme (BMM). It is uncertain whether funds will become available for the follow-on step of pursuing the goal of a biological artificial kidney, which is currently under development within BMM. If follow-on funding fails to materialise, so will the return on previous investment.
- Patients and care providers (other than the physician-researchers in the UMCs) are not currently involved in the development. The Dutch Kidney Foundation intends to increase this involvement in the future. The question is whether it would be better for all stakeholders to be continuously involved throughout the research and development process.

Opportunities

- The increasing numbers of kidney patients means that the market is expanding. This creates the commercial conditions that may allow companies to operate profitably in this market. For patients, this could favour further or faster development of the innovation in question.
- Thanks to government funding, the Netherlands has a firm basis for technological developments in the life sciences. As a result, the country now has substantial potential in healthcare technology development.

Threats

- Innovations in the medical sector are usually subject to a long period of development. Accordingly, those involved need great persistence if they are to stay the course. For this reason, actors are likely to withdraw prematurely, with the result that the innovation in question does not become available to end-users. This could be a reason for the government, or other non-profit organisations, to assume a role in innovations of this kind.
- There is a great deal of uncertainty surrounding the regulations and reimbursements associated with the development of an artificial kidney. With regard to a biological artificial kidney (based on cell material), it is as yet unclear how the pertinent regulations will develop. As a result, there is a risk that development will stall. There is a similar lack of clarity concerning the costs of the innovation and of the new treatment. Initially, the new artificial

kidney will probably be more expensive than traditional dialysis. How should the improved care and quality of life for kidney patients be translated into financial terms? What is the government willing to pay? The government's attitude towards regulations and reimbursements will therefore be pivotal in determining the success of this development.

Case 4: Innovation management at Philips

Strengths

- Philips has put the patient (user) at the centre of the innovation process. Based on patients' needs and experience, it is endeavouring to make progress on eliminating obstacles to product development. New products/technologies will consequently be a better match for users' needs.
- Products are developed in interaction and collaboration with relevant partners, in an 'Open Innovation' setting[57] (alongside users such as patients and care providers, there are also research institutes, health insurers, other companies, and finance providers). This creates more opportunities for delivering technology-based solutions to eliminate any obstacles encountered, since each party can bring their own (complementary) expertise to bear.
- As a major company, Philips can employ people to engage in dialogue with users, and to professionalise this area. This is much harder for an individual research group. In collaborative projects, Philips' partners also benefit in this respect.

Weaknesses

- Companies sometimes have trouble with converting the notion of technology push into demand pull, in procedural terms. In other words, they find it difficult to permanently place users' needs at centre stage. The organisation's traditional focus on technology may sometimes cause it to revert to old patterns of behaviour.

Opportunities

- Professionalisation of the dialogue between researchers and users would also be feasible for individual research groups, if it were conducted in a broader context (e.g. FES projects, the Netherlands Organisation for Scientific Research/Netherlands Organisation for Health Research and Development, and major health funds).

Threats

- If companies get in each other's way (i.e. through excessive competition), working together, or holding partnerships together, may sometimes suffer. Before launching a project, it is vital that the interests of all the parties involved be clearly identified. Once this has been done, they should embark on collaboration only if there is a sufficient basis for trust.
- No expectations should be raised that cannot be met. Accordingly, the issues involved (e.g. disease area, care process, or type of development) and the various parties' present and future expectations must all be clearly identified in advance. A failure to do so effectively may result in disappointments that will ultimately damage the partnership.

Case 5: Therapy for people infected with HIV: HAART

Strengths

- The government set up a special task force to produce a therapy (financial incentive).
- Prestigious scientific journals gave priority to articles on AIDS (scientific incentive).
- There was intensive collaboration between public (National Cancer Institute/ NCI, Duke, US Food and Drug Administration/FDA) and private (Burroughs Wellcome) parties.

Weaknesses

- Originally the raw material (thymidine) was in short supply from private sources (but the NCI made additional raw materials available from its own inventory).
- After market registration there was a lack of clarity about the pricing of the product that had been developed.

Opportunities

- Many white, middle-class Americans soon fell victim to the lethal disease. This helped to create a sense of urgency in the American government (in response to what was seen as a major public health hazard).
- The industry saw a market opportunity and developed a range of other anti-AIDS therapeutics (which are used in combination in the current therapy).

Threats

- If the urgency subsides (as the group of victims shrinks or shifts into another part of society), it is questionable whether a new therapy would be developed as speedily.