rivm

RIVM Report 360020001/2007

Medical devices for small target groups

Availability guaranteed?

J.W.G.A. Pot
A.W. van Drongelen
A.C.P. de Bruijn

Contact:
Jacqueline Pot
Medical Technology Section
jacqueline.pot@rivm.nl

This investigation has been performed by order and for the account of the department of Pharmaceutical affairs and Medical Technology of the Dutch Ministry of Health Welfare and Sports, within the framework of V/360020 Support for Policy on Medical Technology

rivm

rivm

Abstract

Medical devices for small target groups – Availability guaranteed?

The availability of medical devices for small target groups (the so-called orphan medical devices) is not guaranteed in the Netherlands. Orphan medical devices, such as the vertical expandable prosthetic titanium rib for children, are not available upon demand. Various problems have been encountered during the research and development, planning and organisation of manufacturing and reimbursement of such devices. This is the outcome of a study on medical devices for small target groups conducted among stakeholders (patients, healthcare providers, manufacturers and others).

The aim of this report was to provide a first impression of the issues/problems associated with the availability of medical devices for small target groups. The results should be considered as a starting point for further discussion on the necessity to implement measures specifically relating to orphan medical devices.

The study included a worldwide search for the existence of measures designed to stimulate the development and production of medical devices for small patient groups. No such measures are as yet in place in Europe. Various regulatory programmes aimed at supporting the development and marketing of medicinal products and biologicals for rare diseases have been implemented in five regions of the world. Only the USA and Japan have specific regulations for medical devices.

Several measures aimed at fostering the availability of medical products for small target groups are described in this report. Some of these measures are available within the framework of existing policies; other incentives/measures have been proposed by different stakeholders. An example of one such measure is the financial support for experimental products.

To be able to elaborate upon realistic incentives for European orphan medical devices, it is first necessary to establish a uniform definition of an orphan medical device. To this end, a meeting of all stakeholders is recommended – at the national and European level – to determine the parameters of this definition and the feasibility of existing and suggested incentives for orphan medical devices.

Key words:
orphan products, (orphan) medical devices, orphan medicinal products, rare diseases

Rapport in het kort

Medische hulpmiddelen voor kleine doelgroepen – Beschikbaarheid gewaarborgd?

De beschikbaarheid van medische hulpmiddelen voor kleine doelgroepen (zogenoemde wees medische hulpmiddelen) is niet gewaarborgd in Nederland. Een voorbeeld van een wees medisch hulpmiddel is een in grootte verstelbare titanium rib voor kinderen waarvan de borstkas onvoldoende functioneert. Dergelijke hulpmiddelen zijn niet zonder meer beschikbaar, omdat er diverse knelpunten zijn in onderzoek en ontwikkeling, planning en organisatie van de productie en de vergoeding. Dit is de uitkomst van een studie onder belanghebbende partijen (patiënten, zorgaanbieders, fabrikanten en anderen).

Doel van dit rapport is een eerste impressie geven van de problemen rond de beschikbaarheid van medische hulpmiddelen voor kleine doelgroepen. De resultaten kunnen als uitgangspunt dienen voor een verdere discussie over de wenselijkheid maatregelen te nemen.

In het onderzoek is gekeken of er elders in de wereld maatregelen bestaan die de ontwikkeling en productie van medische hulpmiddelen voor kleine doelgroepen stimuleren. Op Europees niveau blijken tot nu toe geen speciale regelingen te bestaan. Vijf landen kennen wel regelingen die het ontwikkelen en op de markt brengen van medicijnen en biologische geneesmiddelen voor zeldzame aandoeningen ondersteunen. Alleen de Verenigde Staten en Japan kennen speciale regelingen voor wees medische hulpmiddelen.

Dit rapport beschrijft welke maatregelen de beschikbaarheid van medische producten voor kleine doelgroepen ten goede kunnen komen. Dit zijn maatregelen uit bestaande regelgeving en maatregelen die de belanghebbende partijen hebben voorgesteld. Een voorbeeld is experimentele producten financieel ondersteunen.

Om verder te kunnen bepalen wat geschikte maatregelen zijn voor wees medische hulpmiddelen, is het noodzakelijk een definitie van deze groep hulpmiddelen vast te stellen. Het is aan te bevelen hierover een bijeenkomst te organiseren voor belanghebbende partijen, op nationaal en Europees niveau.

Trefwoorden:
wees producten, (wees) medische hulpmiddelen, weesgeneesmiddelen, zeldzame aandoeningen

rivm

Contents

rivm

List of abbreviations

AIMDD:	Active Implantable Medical Device Directive (Europe)
CE	Conformité Européenne
COMP:	Committee for Orphan Medicinal Products (Europe)
CVZ:	Dutch Health Insurance Board (College voor zorgverzekeringen)
EMEA:	European Agency for the Evaluation of Medicinal Products
EU:	European Union
FDA:	Food and Drug Administration (USA)
HDE:	Humanitarian Device Exemption (USA)
HUD:	Humanitarian Use Devices (USA)
IRB:	Institutional review board (USA)
IVDD:	In Vitro Diagnostic Medical Devices Directive (Europe)
J-NDA	Japanese New Drug Application
MDD:	Medical Device Directive (Europe)
NIH:	National Health Institute (USA)
ODA:	Orphan Drug Act (USA)
OOPD:	Office of Orphan Products and Development (Europe)
PMA:	Pre market approval (USA)
R&D	Research and development
RIVM:	National Institute for Public Health and the Environment
TGA:	Therapeutic Good Administration (Australia)
TPP:	Therapeutic Products Program (Canada)
UN:	United Nations
USA:	United States of America
VWS:	Dutch Ministry of Health, Welfare and Sport
WHO:	World Health Organization
ZN:	Dutch Branch organisation for Health Insurers (Zorgverzekeraars Nederland)

1 Introduction

1.1 Availability of health technologies

During the last decades, health care has improved enormously through the development of new health technologies. Still, in a market driven economy, manufacturers may have little or no interest in developing products which benefit a very small, but needy, segment of the population. These kinds of products might not appear on the market as a manufacturer foresees that the financial return will not exceed the costs for research, development and market introduction. This could result in a market gap, referred to as the 'orphan problem': people in need of help will not have access to the necessary products because they are simply too few. Throughout the world, different approaches exist to stimulate the knowledge and treatment of rare diseases. These so-called 'orphan programmes' have been instituted in several countries and regions.
In Europe, a specific programme for orphan medicinal products exists, but for medical devices intended for small patient groups there has been no specific attention, up to now. The Dutch Ministry of Health, Welfare and Sport (VWS) shows an increasing interest in the rational development and use of medical technology. Apart from this project on orphan medical devices, the Ministry of VWS is involved in two other related projects, namely 'priority medical devices' and 'essential health technologies.' Priority medical devices are defined by the World Health Organization (WHO) as 'gaps in the range of diagnostic, therapeutic and assistive medical devices available in the market that could be filled with devices, which have a high impact on global burden of diseases or disability burden'[1]. Essential health technologies are defined as 'absolutely necessary health related technologies to reach the United Nations (UN) Millennium Development Goals'. Health related technologies are physical, biological or chemical devices, clinical procedures and services that have been developed to improve health. They are considered to be essential when they are evidence based, cost-effective and meet priority public health needs[2].
Dependant on the degree of economic development, a country needs to tackle these issues. This is presented schematically as a pyramid shape in Figure 1.

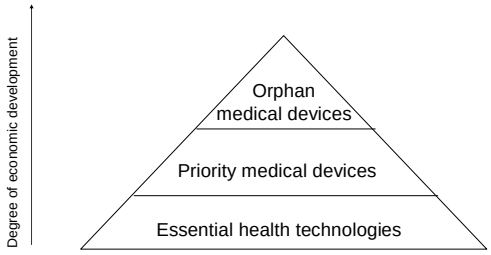

Figure 1: Schematic representation of the different categories of technologies

In developing countries, it is of utmost importance to provide for essential health technologies. In more developed countries one expects such technologies to be present. In these countries the identification of priority medical devices will assist in policymaking to remedy possible gaps and to justify public spending. The WHO has taken up responsibility for the investigation of the essential health technologies and the priority medical devices. These investigations are currently going on.

From a social ethical point of view, people in well developed countries should not be denied medical care only because their condition is rare. Therefore the development of orphan medical devices should not be hampered.

1.2 Objectives and scope

The Ministry of VWS asked the Dutch National Institute for Public Health and the Environment (RIVM) to answer the following questions for the Dutch situation:

- ***Are there impediments to market medical devices for small target groups in current practice?***
- ***If impediments exist: What can be done to foster the availability of medical devices for small target groups?***

For the purpose of this project orphan medical devices are defined as devices which benefit a small segment of the population. This definition is stated in general wordings in order to be as little restrictive as possible and to allow an open view to potential problems.
The result of the study provides an overview of possible orphan issues for medical devices. This knowledge can than be taken as a starting point for further discussion on the necessity to take measures to improve the availability of medical devices for small patient groups.

2 Method

This study took place in three phases (see Figure 2). First, a conceptual framework with important stages within the lifecycle of a medical product was formulated to be able to specify the orphan problem. The framework made it possible to sort any impediments within the process necessary for a medical product to become available. Some impediments may be inherent in the nature of the product. Other impediments, or the same impediments in a different magnitude, might be directly connected with the orphan problem. General characteristics of a medical products lifecycle were described on the basis of information from literature and personal expertise. The term 'medical product' refers to both medicinal products and medical devices.
In the second phase of the study, the existing programmes for orphan medical products were identified by performing desk research (studying literature, including articles, reports and legislation). Pubmed and Google were used as search engines using the terms 'orphan product', 'orphan medical device', 'paediatric medical device' and 'orphan drug'. Medicinal products were deliberately included in this project, because the legislation for medicinal products is often older and more mature than medical device legislation. If orphan initiatives exist they are more likely to have been established in drug regulations.
In the third phase of the study, Dutch players in the field of medical devices were consulted, either by interviews or by using an e-mail questionnaire. The demand for orphan medical devices was examined by questioning patient organisations and representatives of care providers. The barriers to develop orphan medical technologies were examined by questioning representatives of the medical device industry and other experts in the field. Barriers and incentives found were appointed to the conceptual framework as far as possible.

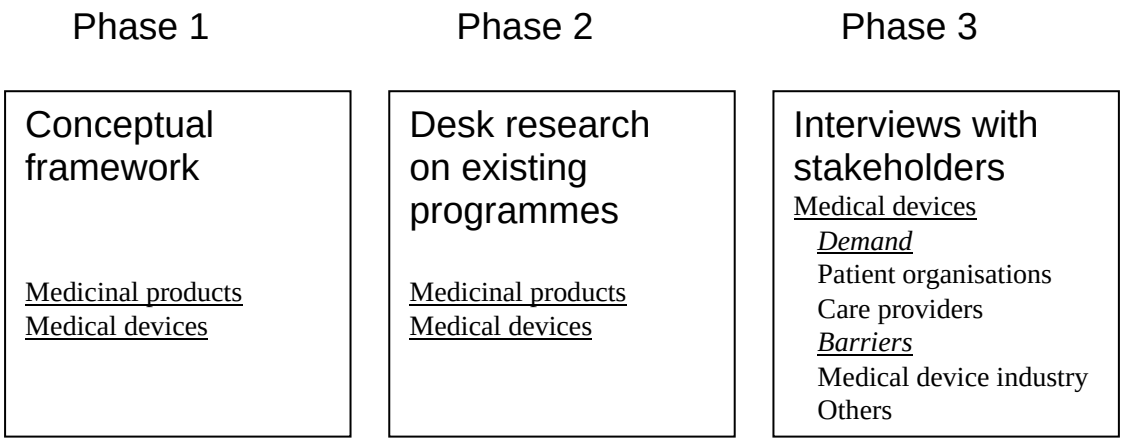

Figure 2: Schematic representation of the phases within the project

3 A conceptual framework

This chapter describes the conceptual framework as formulated by the authors of this report (paragraph 3.1). The framework is described in such a way that it is applicable to medical devices as well as to medicinal products. However, as a consequence of differences in their nature, they might move differently through the framework. This will be addressed in paragraph 3.2.

3.1 The life cycle of a medical product

The conceptual framework consists of stages within the life cycle of a medical product. The framework is derived from Goodman[3], a senior scientist chairing a workshop session of a roundtable on research and development of medicinal products, biologicals and medical devices, organized by the American Institute of Medicine. He described five main streams or pathways of activity for the industry: (1) regulation, (2) research and development, (3) planning and organization of manufacturing, (4) promotion and education, and (5) legal. For the purpose of this project, several pathways were put together ('regulation' with 'legal' and 'planning and organization of manufacturing' with 'promotion and education'). Reimbursement was added as an extra stage, resulting in four stages, which are not necessarily sequential or mutually exclusive.

1. **Planning and organization**
   In parallel to the actual production process, other streams of activity are necessary. These usually start with market research on user needs, competition, and other factors that can influence the product (e.g. the types of health and economic evidence required to demonstrate the value of the technology in the next stages of the framework).
   It is also important to plan education and promotion activities. These activities can begin after research and development and before market approval. It means preparing the target markets and informing those who will be in a position to order and use the medical product. Sales, distribution, and customer support functions must be in place. For orphan products, the magnitude of education and promotion activities is probably quite small, since it is likely that the few patients and care givers concerned are already involved early in the process. Still, these activities are mentioned here, because it remains important for the planning and organization of a company.
2. **Research and development (R&D)**
   This stage is the process that starts with generating ideas and concepts and ends with properly functioning products. It includes developing prototypes, preclinical testing and clinical testing in iterative steps.
3. **Regulatory pathway (general legal aspects, market approval and post marketing surveillance)**
   Legal considerations must be managed throughout the medical products life cycle, including market clearance, permission to conduct clinical testing/evaluation, obtaining patents, licensing, maintaining patient protection, and protection against product liability. Medical products have to meet legal requirements to gain market approval. Also post market surveillance is mandatory to gather data about the experiences and incidents in the field. This is a prerequisite for the continuous cycle of improvement and it provides information for further marketing efforts.
4. **Reimbursement**
   Requisites for reimbursement of medical products differ from country to country, but generally speaking, outcome data and health economic evidence become more and more important for decision makers.

3.2 The nature of medicinal products and medical devices

Some impediments in a medical products life cycle may be inherent in the nature of the product. To be able to understand the impediments related to the orphan problem, described later in this report, this paragraph will address the nature of medicinal products and devices and their differences per stage of the framework.
It is hard to generalize for all medicinal products and devices, since there are many different kinds of medicinal products and the field of medical devices is even more diverse. Medical devices cover a wide range of products varying from very simple to complex: e.g. wound dressings, thermometers, prostheses, orthoses, active implantable devices, anaesthetic/respiratory devices, dental devices, imaging equipment and surgical instruments. Despite the difficulty to generalize, several authors state that medicinal products and devices are very different by nature[3,4,5,6,7].

1. **Planning and organization**
   The medical device industry is, in contrast to the pharmaceutical industry, characterized by a small number of large multinationals and a large number of small entrepreneurial companies that supply niche markets[3,6]. While these small companies are largely focussed on gaining 'proof of concept' and overcoming initial regulatory impediments, they tend not to have the staff, experience, and other resources needed to manage the different pathways in a device life cycle. Further, since they tend to have a limited product range that can sustain their cash flow, their economic risk profile is more closely tied to the success of one or a few products. As such, the viability of these companies is highly sensitive to changes in regulations, payment/reimbursement requirements, sales and distribution, manufacturing capacity, and other factors that can divert their limited resources[3]. Recovering the investments for medical devices needs to take place within a shorter timeframe than for medicinal products. The initial product is likely to be improved several times during its lifecycle. Accordingly, the life cycle of a device can be as short as 18-24 months, which is considerably less than that of medicinal products[4]. The average time to discover and develop a new drug takes about ten to twelve years[8]. Compared to medicinal products the incremental improvements of medical devices often take place against higher costs[5].
2. **Research and development**
   For medical devices, the European regulation requires confirmation of the fulfillment of the safety and effectiveness requirements. This confirmation must be based on clinical data. The manufacturer is given the choice that the clinical data is based on:
   - either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed as well as, if appropriate, a written report containing a critical evaluation of this compilation;
   - or the results of all the clinical investigations performed.

   By contrast, new drug applications generally must contain evidence of efficacy from two randomized, controlled clinical trials[6]. Performing clinical assessments for medical devices is less developed compared to medicinal products [4,5,6,7]. Several factors, related to the research and development of medical devices, contribute to the lack of clinical evaluation data. Perhaps the most important factors are the inherent constraints when designing device trials to prove efficacy. The large scale blinded, randomized, placebo controlled trials common in medicinal products studies are often extremely difficult or unrealistic to perform for medical devices [6,7]. More specifically, the reasons may be **limited possibilities to**:
   - design a placebo treatment and to blind clinicians and patients,
   - recruit patients [4,6,7],
   - recruit skilled clinicians[6],

- recruit volunteers for an experimental treatment, especially when the device involves an invasive procedure[6],
- perform long term follow-up studies[6],
- use a clear cut outcome measure (obvious gains in mortality or morbidity, so-called 'hard endpoints' might be lacking and even clinically useful intermediate endpoints, such as blood pressure or cholesterol levels, are often unavailable for devices[3]),
- isolate the health impact of the device from its surrounding procedure or user relationship[6].

3. **Regulatory pathway**

   The marketing authorisation of all medical devices is regulated by three European directives: the Medical Device Directive (MDD)[9], the Active Implantable Medical Device Directive (AIMDD)[10] and the In Vitro Diagnostic Medical Devices Directive (IVDD)[11]. These directives are based on specified conformity assessment procedures. The manufacturer should demonstrate compliance with essential requirements for safety and performance. Depending on the risk classification of the device, none, limited or extensive involvement of a Notified Body is required. After successful completion of these procedures, it is allowed to affix the CE (Conformité Européenne) mark to the product. All medical devices placed on the European market must bear a CE-mark. Once a medical device carries a CE mark, it can be freely marketed within the European Economic Area (EEA).

   The marketing authorisation of medicinal products is regulated by the medicinal products Directive[12]. An application has to be made to the European Medicines Evaluation Agency[13] or with a national competent authority for medicinal products, depending on the type of product. After an assessment procedure, during which a dialogue with the manufacturer usually takes place, registration implying market approval may be achieved if all concerns from the authorities have been addressed appropriately.

4. **Reimbursement**

   For medicinal products a lot of experience has been gained throughout the world with pharmacoeconomics. Cost-effectiveness data play more and more an important role. It may be expected that for medical devices decision makers may want information on cost effectiveness as well to make rational choices within a limited health care budget.

4 Results from desk research

This chapter first describes the existing programmes for orphan medical products per region (paragraph 4.1). Second, the existing orphan programmes will be discussed in relation to each other (paragraph 4.2).

4.1 Existing programmes for orphan medical products

The literature search led to two review papers on existing policies for orphan medical products[14,15]. The regions indicated as having established programmes to support the development and marketing of products for rare diseases are: the United States of America (USA), Japan, Australia, Canada and the European Union (EU). Major features of the different programmes will be outlined in this paragraph. Table 1 presents an overview of the programmes discussed. Canada is not in table 1, since this country has no stand-alone orphan product regulation. Still, access to products intended to treat rare disorders can be gained through alternate mechanisms that have been implemented within existing policies and regulations[14]. These mechanisms will be described in subparagraph 4.1.2.

Table 1 International policies on orphan products

Region	United States		Japan	Australia	European Union
Products	Medicinal products and biologicals	Medical devices	Medicinal products, biologicals and medical devices	Medicinal products and biologicals	Medicinal products and biologicals
Date established	1983	1996	1993	1998	2000
Legal framework	Orphan Drug Act	Humanitarian Use Devices	Orphan Drug Regulation	Orphan Drug Policy	Regulation (EC) No 141/ 2000
Administrative authorities involved	FDA/OOPD	FDA	MHLW/OPSR	TGA	EMEA/COMP
Number of orphan products designated / approved*	1730 designated 309 approved	43 HUD exemptions	Medicinal products: 143 designated 66 approved Med. Dev.: 7 designated 2 approved in May 2000[14]	130 designated 44 approved	34 designated 432 approved
Consulted websites (August 2007)	www.fda.gov/orphan/DESIGNAT/alldes.rtf www.fda.gov/orphan/DESIGNAT/allap.rtf	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm		www.tga.gov.au/docs/html/orphand2.htm	ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm

* Designated: the status of an orphan product was granted
Approved: authorized and registered as an orphan product
The consulted websites for providing these figures are presented one row lower in the table

4.1.1 The United States of America

In 1983, the USA launched an orphan products programme. More than 300 medicinal products and biological products for rare diseases have been brought to the market since then. The Office of Orphan Products Development (OOPD) promotes the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. The OOPD administers the major provisions of the Orphan Drug Act (ODA) which provide incentives for sponsors to develop products for rare diseases. In addition, the OOPD administers the Orphan Products Grants Program which provides funding for clinical research on rare diseases. The requirement for designation a drug as an orphan drug is that the disease or condition (A) affects less than 200,000 persons in the USA, or (B) affects more than 200,000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will recovered from sales in the United States of such drug[16].

To provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting small numbers of patients, the USA Food and Drug Administration (FDA) issued a final rule regarding humanitarian use devices (HUDs)[17]. This regulation became effective on October 24, 1996. The regulation provides for the submission of a humanitarian device exemption (HDE) application, which is similar in both form and content to a pre-market approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. An HUD is exempt from the effectiveness requirements if:

1. it is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the USA per year (approximately 1.33 per 100,000 citizens);
2. it would not be available to a person with such a disease or condition unless the exemption is granted;
3. no comparable device is available to treat or diagnose the disease or condition; and
4. it will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

No person granted an exemption with respect to a device may sell the device for an amount that exceeds the costs of research and development, manufacture, and distribution of the device.

Devices granted an exemption may only be used:

a) in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices in the facilities, and
b) if, before the use of a device, an IRB approves the use in the treatment or diagnosis of a specific disease or condition, unless a physician determines in an emergency situation that approval from a local IRB cannot be obtained in time to prevent serious harm or death to a patient. In special cases in which a physician uses a device without an approval from an IRB, the physician shall, after the use of the device, notify the chairperson of the local IRB of such use. Such notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

October 2007, 41 devices were approved as orphan (see Annex I). If a device no longer fulfils the HUD-requirements, it has to apply for a ‘normal’ market approval. The list of HUDs will therefore change in time.

These strict rules for an HDE-application led to some concerns noted by clinicians and industry[18]. One concern was that the HDE process is restrictive and difficult to understand. It was stated that the limit of 4,000 patients is arbitrary and overly restrictive. Also they noted that the IRBs are unclear about how to handle HDEs, and insurance companies may not cover their use because they are uncertain whether

these devices should be treated as investigational or approved. Also the requirements for the IRBs and the value it adds to the use of the device were questioned. The FDA has already approved the device for marketing. Furthermore, the restriction on profit making was pointed out as a key economic barrier to the development of paediatric devices. The requirement for an independent certified public accountant to verify that no profit is being made was noted as a further deterrent for the use of this regulatory path.

4.1.2 Canada

The Therapeutic Products Programme (TPP) is the Canadian regulatory system that evaluates and monitors the safety, efficacy, and quality of medicinal products, medical devices, and other therapeutic products available to Canadians. The TPP must ensure that medicinal products and medical devices meet strict regulations and high standards before the products are made available to Canadians.
A review held in 1996 determined that existing laws and regulations ensure access to critical medical products[15]. Canadians can obtain access to essential medicines, including medicinal products intended to treat rare disorders, through alternate mechanisms that have been implemented within existing policies and regulations. These include the Special Access Program, Investigational New Drugs/ Clinical Trials, Priority Review, Notice of Compliance with Conditions, and Importation of Drugs for Personal Use.
Tax incentives and grants are available for qualified research and development in Canada. Several types of government fees can also be dramatically reduced for medical products with limited use or low sales. The Submission Evaluation Fee can be reduced to 10% of anticipated sales over a three-year verification period. Standard patent protection for pharmaceuticals is also in place in Canada, for 20 years from the date of filing. Patents can be granted for new inventions or novelties for a function.

4.1.3 Australia

The Australian orphan medicinal products programme was established and started on January 1, 1998. The Therapeutic Goods Administration (TGA) developed the programme with the assistance and cooperation of the USA Office of Orphan Product Development (OOPD). This led to an Australian program largely based on that of the OOPD, except for its tax and funding incentives, and marketing exclusivity.
The incentives of the Australian program are fee waivers and priority evaluation. Protocol assistance and advice about applications are provided on request as for other prescription medicinal products. As within the USA programme, the TGA does not accept the registration of a second orphan drug for the same indication unless the second drug is shown to be clinically superior. The program does not include orphan medical devices.

4.1.4 Japan

The first notification to the industry regarding systems to promote the development of orphan medicinal products in Japan appeared in 1985. This notification allowed applicants to submit a simplified Japanese New Drug Application (J-NDA) for orphan medicinal products. The current programme resulted from a change to the Pharmaceutical Affairs Law in 1993[14] and aims at medical devices as well. In Japan the criteria for orphan product designation are:

1. The disease to be treated must be serious and rare.
2. It must affect fewer than 50,000 people in Japan (approximately 40 per 100,000 citizens).
3. Its treatment must be a high priority in health care.
4. There should be no alternative medicinal products or other interventions available, or
5. The new product must be anticipated to be significantly safer or more efficacious than existing medicinal products and interventions.
6. Most importantly there should be a high possibility of development of the product. There must be a theoretical basis for the application and a feasible development plan.

Given these requirements, it is difficult to obtain designation when the product is just at the preclinical developmental stage. Orphan drug designation is given to the combination of the following: the applicant (usually a pharmaceutical company), the product, and the indication (intended use). Incentives for the promotion of orphan product development in Japan are:

- Orphan product development grants.
  This governmental grant cannot exceed 50% of the research and development costs per year and is available for a maximum of three years after designation. Therefore the company should determine the best time to request designation.
- Consultation on protocols, development, and preparation of J- NDA.
- Authorization of R&D costs for tax deductions.
- Fast track reviews for J-NDA approval.
- Accelerated review process.
- Reduced J-NDA application fee (5,2 million yen vs. 8 million yen).
- Extension of re-examination term. The period before a generic drug can enter the market is related primarily to the re-examination term. During the re-examination period a generic drug cannot enter the market unless the second applicant provides all original data (it cannot reference the first company's data or application). For a new chemical entity the re-examination period is normally six years; for orphan medicinal products this is extended to ten years. Devices are normally re-examined after four years but this is extended to seven years for orphan medical devices.

4.1.5 The European Union

The European Union (EU) has provided specific legislation for orphan medicinal products. The Regulation on Orphan Medicinal Products came into force on January 22, 2000[19] and the implementing regulation on April the same year[20]. To implement the legislation and to stimulate the development of orphan medicinal products the Committee for Orphan Medicinal Products (COMP) has been established within the European Agency for the Evaluation of Medicinal Products (EMEA). The COMP can grant orphan designation for a drug or biological product if the following criteria are met:

1. The product is intended for a disease with a prevalence less than 50 per 100,000 citizens in the European Union, or without incentives it is unlikely that the marketing of the product (intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition) would generate sufficient return to justify the necessary investment, and,
2. There exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Incentives of the Regulation include:

- Access to the centralized procedure for European registration.
- Ten years of market exclusivity. Six of these years are guaranteed; however, exclusivity can be lost after that time if the prevalence of the disease has increased beyond the orphan limit, or if a similar, clinically superior product for the disease becomes available.
- The manufacturer can ask the COMP for advice on how to set up research protocols and the assessment request.
- The manufacturers can request for application fees to be waived or reduced.
- Financial incentives centrally available (like research grants) and/or financial incentives available in individual member states (like favourable tax treatments or adjusted reimbursement criteria).

In 2005, the COMP evaluated the European legislative framework for orphan medicinal products and concluded that this framework is suitable to achieve public health benefits for patients suffering from rare diseases[21]. Every member state has to take national measures for the benefit of orphan medicinal products. In the Netherlands, the minister of Health, Welfare and Sport appointed a Steering Committee Orphan Medicinal products (in Dutch: 'Stuurgroep Weesgeneesmiddelen') in April 2001. The mission

of this committee is to encourage the development of orphan medicinal products and to improve the situation of patients with a rare disease, especially to strengthen the transfer of information on rare diseases. Among other things, this steering committee works on a database with information on registered medicinal products for rare diseases.
For orphan medicinal products a new rule became effective in the Netherlands in the year 2006. With this rule, the Dutch government stimulates the availability of orphan medicinal products by limiting the amount of money hospitals have to spend on orphan medicinal products out of their general budget.
Recently, a new European regulation came into force which aims to improve the health of children by ensuring that medicines used to treat children are appropriately tested and authorised[22]. It also aims to stimulate research and development of medicines for use in children. The manufacturers of these products are granted an extra half year of patent exclusivity.
In Europe, no regulation has been developed to grant incentives to the medical device industry to stimulate the marketing of orphan medical devices or medical devices specific for children. The MDD[9,10,11] regulates placing on the market of all medical devices, irrespective of the target group or frequency of use.
The exemption in the MDD for so-called ‘custom made devices’ may be relevant for the discussion of orphan medical devices. These devices are ‘specifically made in accordance with a duly qualified medical practitioner’s written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient’. Examples of custom made devices are dental appliances, artificial eyes and hearing aid inserts. The manufacturer of custom made devices in general follows the same registration principles as the lowest risk class (class I) of the medical devices. So, the manufacturer himself has to state that the product fulfils the essential requirements and that the product is manufactured for a specific patient. In addition, the manufacturer should put together documentation in which the design, the manufacturing process, and performances of the product are described. This documentation does not have to be reviewed by a Notified Body, which lessens the manufacturers’ work within the CE-marking process considerably.

4.2 Discussion

The USA, Japan, Australia, Canada and the European Union have established programmes to support the development and marketing of products for rare diseases. In Canada, there is no stand-alone programme specifically for small target groups. The other regions have specific programmes for orphan medicinal products and biologicals. Only the USA and Japan have specific arrangements for medical devices as well (see table 1).
Considering all orphan programmes, the number of products designated and approved as orphan medical products are small and differ between regions (see table 1). This difference will be partially due to the differences in the requirements for designation as an orphan product between regions (see table 2). The most striking differences are those between the prevalence thresholds for designating the orphan status to a product, between regions as well as between products. The prevalence threshold in the USA for the designation of an HUD-exemption is 4,000 patients, which is considerably less than the USA threshold for the designation of an orphan drug (200,000 patients). There is no explanation for this difference. The number of 4,000 was decided by the U.S. Congress along with members of the Center for Devices and Radiological Health at FDA[23].
Given the fact that manufacturers make use of the existing incentives, it can be concluded that they are willing to invest in economically less attractive products.
Table 3 contains an overview of the incentives present in the existing programmes. These incentives are appointed to the stages of the framework as formulated within this project.

1. **Planning and organization**
   The success rate for manufactures to sell will be increased by market exclusivity. This kind of incentive provides a more stable market, lessening the insecurity about return on investment, which could make planning and organization easier. Market exclusivity is based on normal patent protection in all regions. However, in Japan the time until generic competition is allowed, is primarily defined by a re-examination period, which is extended for orphan products.
2. **Research and development**
   Except for Australia, all of the investigated regions use incentives concerning cost reducing policies for R&D. Government grants for research and development on orphan products are available in the USA, Japan, Canada, and the EU.
3. **Regulatory pathway**
   Within the regulatory pathways, incentives aim at reduction of application fees in all of the regions. The USA also provides the possibility to gain an exemption from effectiveness requirements and assessments are given priority and may be shorter in practice.
4. **Reimbursement**
   In the Netherlands the availability of orphan medicinal products is stimulated by limiting the amount of money hospitals have to spend out of their general budget.
   In the USA, there is an incentive in the R&D stage which has a negative influence at the reimbursement stage, i.e. the HDE may lead to an unclear status (is the product investigational or approved?), making it difficult to get a product reimbursed.

Table 2 Requirements for designation as an orphan product

Requirement	United States		Japan	Canada	Australia	European Union
	Medicinal products and biologicals	Medical devices	Medicinal products, biologicals and medical devices	No stand alone programme	Medicinal products and biologicals	Medicinal products and biologicals
Prevalence of the condition OR	Less than 200,000 (75 per 100,000)	Less than 4,000 (1.33 per 100,000)	Less than 50,000 (40 per 100,000)	Not applicable	Less than 2,000 (11 per 100,000)	Less than 185,000 (50 per 100,000)
Financial return on product AND	If costs can not be recovered	No; Restriction on profit making	No	Not applicable	If costs cannot be recovered	If costs cannot be recovered, return considered over 7 years
Nature of disease/ disorder	Rare only	Rare; no other treatment; Benefits > Risks	Rare and serious disease; no other treatment; high efficacy or safety	Rare (not further defined)	Rare only	Life threatening or chronically debilitating; no alternative treatment
Time of applications	Designation before application to market	After FDA approval	A high possibility of development is required.	Before marketing	Not known	Not known

Table 3 Incentives

Stage	Incentive	United States		Japan	Canada	Australia	European Union
		Medicinal products and biologicals	Medical devices	Medicinal products, biologicals and medical devices	No stand alone programme	Medicinal products and biologicals	Medicinal products and biologicals
Planning & organization	Market exclusivity	7 years – Prevents same product being approved for the same indication unless clinical superiority is shown.	No	Re- examination period extended from 4 to 10 years (devices 4 to 7 years and medicinal products 6 to 10 years).	Standard patent protection for medicinal products for 20 years from the date of filing. Patents for new inventions or novelties for a function.	5 years, similar to other medicinal products. A second product with the same active ingredient will not be designated unless clinical superiority is shown.	10 years The period may be reduced from 10 to 6 years if the product looses the orphan status.

Stage	Incentive	United States		Japan	Canada	Australia	European Union
		Medicinal products and biologicals	Medical devices	Medicinal products, biologicals and medical devices	No stand alone programme	Medicinal products and biologicals	Medicinal products and biologicals
Regulatory pathway	Regulatory fee waivers	New Drug Application / Biologicals License Application fee waived; product or establishment fee waivers must be requested.	No	Application fee reduced	Submission evaluation fee can be reduced to 10% of anticipated sales over a 3-year verification period. Government fees can be reduced as well for medical products with limited use or low sales.	Marketing application and orphan designation fees waived; other fees can be reduced.	Marketing application and designation fees can be reduced or waived.
	Expedited assessment	Shorter in practice	No	Priority given	Priority review	Priority given	Member state specific
	Exemptions from certain requirements	No	An exemption from effectiveness requirement.	No	Special access programme Medicinal products for personal use	No	Custom made devices involve an exemption from a review by a Notified Body.
Research & development	Grants for research	Clinical studies only; pharma and academia eligible (NIH and others)	No	Clinical & non- clinical studies; pharma only eligible	Investigational new medicinal products / clinical trials.	No	Biomed and national measures
	Tax credits	50% for clinical studies	No	6% of both clinical and non-clinical studies and limited to 10% of the company's corporation tax.	Yes	No	Member state specific
	Protocol assistance	Provided under the Act	No	On request		On request	Provided under the Regulation
Reimbursement	Reimbursement during an investigational period	No	No	No	No	No	Only in The Netherlands

5 Results from interviews

In this chapter, we describe the results obtained by interviewing several Dutch players in the field of medical devices (see list Annex II). Two main questions were addressed:

1) Can you think of impediments in the development of products for rare diseases or minority groups (such as children). If so, which products or groups of people do you have in mind?
2) Which are incentives for the development of devices aimed to treat or diagnose conditions that affect only a small number of people?

In this chapter the products, impediments and incentives mentioned will be described per stakeholder in the first paragraph (5.1). The second paragraph (5.2) contains conclusions from the interviews appointed to the stages in the lifecycle of a medical product.

5.1 Products, impediments and incentives mentioned by stakeholders

The interviewed persons can be divided in the following groups of stakeholders: patients, care providers, medical device manufacturers, and other experts. This paragraph contains subparagraphs with summaries of the interviews per stakeholder group and each subparagraph starts with a textbox containing the medical devices mentioned as orphans by that particular group of stakeholders.

5.1.1 Patients

Medical devices mentioned as orphans by patients

- custom made devices (orthopaedic shoes, hearing aids)
- several kinds of neuro-stimulation techniques
- assistive devices

In order to gain insight into the need and demand of patients representatives of two patient organisations were interviewed.
An interview was held with a representative of the Dutch Genetic Alliance (VSOP: Vereniging Samenwerkende Ouder- en Patiëntenorganisaties). The VSOP is an umbrella organization of about sixty Dutch, disease-linked, parent and patient organizations, most of them concerned with genetic and/or congenital disorders. One of their main fields of interest is ‘Rare Disorders’. In their opinion, ‘orphan medical devices’ is not an issue at the moment. This is probably due to the fact that devices can be used for more than one (orphan) disease or condition. In this way, the disease treated can be designated as ‘orphan’, but the device itself cannot.
The researchers also spoke with a representative of the Dutch association for chronically ill and handicapped persons (CG-raad). This is an umbrella organization with more then 150 member organizations. During the interview with the representative of the CG-raad, the main attention was given to the reimbursement system, because, according to him, it is difficult to get reimbursement for new products and especially for products which are only intended for a small group of people. A transparent research budget for insurance companies in order to study the effectiveness for these kinds of products would be favourable. According to the representative of the CG-raad, the medical devices mentioned as orphan, need to be tested in what he called ‘experience based research’ instead of ‘evidence based research’. It was also mentioned that the medical device companies producing these devices (for chronically ill and handicapped persons) often are small companies operating in a competitive field. A close cooperation between universities and companies would probably be helpful.

5.1.2 Care providers

Medical devices mentioned as orphans by care providers

- advanced communication aids
- advanced upper limb prosthesis
- robot manipulator
- swim/neck collar for children
- a shower stretcher for transfers in and out of a swimming pool for people who cannot sit
- a hoist with an abdominal frame for the transfer of a patient in an orthoses
- a device supporting crawling for patients with severe tetra pareses or for patients with severe lung problems

Thirteen persons working in a clinical setting were approached by e-mail. Three persons responded. A rehabilitation doctor did not agree with the strict rules on clinical investigation data before market approval. He mentioned that it is impossible for medical devices to provide for evidence based effectiveness data. One reason was that medical device companies are often small companies and therefore not able to bear the research costs. Another reason he mentioned was that the number of patients are often too small to perform a proper study.
A medical technology consultant of a university hospital mentioned that once in a while orthopaedic instruments are adapted for complex or rare treatments / fractures. He also mentioned a custom made device: a breathing device connected to a wheelchair for (mostly terminal) children with a muscle disease (actually, this is not a new medical device but a combination of devices). A uniform solution would not be possible because of the many different types of wheelchairs and different types of breathing devices. In his view, these kinds of devices take up extra time and money to develop and, according to him, insurance companies are not eager to reimburse them. Payment mostly comes down to the hospital or the patient. The association of occupational therapists confirms this. They mentioned several custom made devices which are hard to get.
The interviewed persons from a clinical setting formulated three suggestions to stimulate the availability of medical devices for small target groups:

1. An independent organization should assess individual applications for reimbursement of a certain device. The assessment should result in a binding advice to reimburse or not. The insurers should act accordingly. A committee with representatives of all stakeholders should develop a decision model.
2. Insurance companies should be forced to reimburse custom made devices if there is no such device on the market.
3. A website or database for health care organisations, universities and companies with information on orphan products could provide a total picture of possibilities. People would know where to turn to with specific needs.

5.1.3 Medical device manufacturers

Medical devices mentioned as orphans by manufacturers

- Several patients with a spinal cord injury could benefit from certain devices (not specified). There are about 10,000 spinal cord injured patients in the Netherlands. This means that about 3 per 100,000 citizens
- Facial prosthesis for patient missing part of their skull due to a brain tumour (25-50 patients yearly).
- Custom made knee prosthesis for patients with knee tumours.
- Pumps for the treatment of pulmonary hypertension.
- Implantable insulin pump.
- Several kinds of neural stimulation techniques
- Intervertebral disc

Products especially for children:

- Special pacemakers and wires for newborns and small children with cardiac arythmea
- Orthoses
- Vertical Expandable Prosthetic Titanium Rib
- Ostomy bags

To investigate whether orphan medical devices are an issue according to the Dutch medical device industry, the authors of this report asked the Dutch branch organisations to gather information.
The Federation of Technology Branches (FHI: Federatie Het Instrument) sent its 120 members a questionnaire by e-mail. Eight companies responded that they noticed problems with orphan medical devices. Six of them were approached to obtain further details by an in-depth interview.
In addition, the Dutch Federation of manufacturers, importers and traders of medical products (Nefemed) also asked its members if they experienced problems with 'orphan devices' and compiled the answers in an e-mail.
One manufacturer of medical devices mentioned that he did not place a product on the market, because the costs for the CE-marking were considered too high for the expected small number of buyers.
Another company indicated that EMC testing of prototypes is very costly, especially when the prototype changes several times. This is a serious impediment for placing a product on the market when the number of patients is low.
Another manufacturer mentioned that for a product with a display, he could not fulfil the language requirement as stated in the Dutch implementation of the MDD (Besluit medische hulpmiddelen), because this product was used by a very limited number of people. Therefore, the messages were only in English, which the manufacturer considered to be acceptable, because the messages were translated in the Dutch manual and the patients were well trained in the use of the device. For manufacturers it is important to know that they can apply for an exemption of the language requirements. Although this problem was only mentioned once, it can be argued that the language requirement might be an impediment for 'orphan' devices, especially if a product requires an extensive manual.
Several companies mentioned that the main impediment they experienced was the reimbursement system. Some products are not refunded, because they are not covered by the standard health insurance package or some products are more expensive than the standard refund for a diagnosis related group, which means that the hospital looses money when supplying that product. However, it is stated by the manufacturer that these products would lead to cost savings for the society after a longer period of time and therefore considered an economically unsound situation. Other companies mentioned that they were only reimbursed a standard low reimbursement tariff for a complex product. These products were claimed to have advantages over the standard product, e.g. a higher percentage of complete recovery. It

was mentioned that several of these products were withdrawn from the market due to the low reimbursement tariff.
Some companies also supplied products not entitled for standard reimbursement. These products can be reimbursed on a case-by-case basis. However, this requires an extra effort because each individual case needs to be assessed.
Until recently, it was not quite clear how to get a product (category) in the standard health insurance package. At the moment, it is a high priority of the Dutch Health Insurance Board (CVZ: College voor zorgverzekeringen) to bring more and more transparency in the assessment procedures.
Obtaining a place on the reimbursement list means that, after the development stage, there is an additional period of costs without income. Moreover, the reimbursement decision after this investigation can be negative. Considering that most of the companies making new products are relatively small, they might be unable to survive this period.
The manufacturers fear an obligation to meet high level criteria like evidence based effectiveness and cost effectiveness, which is almost impossible in their view. It is a general problem for all medical devices, but it is likely to be more of an impediment for orphan medical devices, because of the difficulty to perform a proper clinical investigation with a small target group.

The consulted manufacturers did three suggestions to stimulate the availability of medical devices for small target groups:

1. Create financial support for developing experimental products.
2. The reimbursement authority should consider accepting less elaborate studies to support the (cost-) effectiveness in case of small target groups.
3. A possible solution for small companies to survive during the investigational period may be to reimburse their orphan products temporarily and decide upon the continuation of the reimbursement afterwards.

5.1.4 Other experts

Medical devices mentioned as orphans by other experts in the field of medical devices

- Blue lamps
  for the syndrome of Criglernajjar. One or two people in the Netherlands are suffering from it. These lamps can be used for other purposes as well.
- Cooling vests
  for ectodermial dysplasia. These vests might also be helpful for other indications. The effectiveness of cooling vests for MS patients is under investigation at the moment.
- Robot manipulator

Also other experts were consulted, a few persons from the CVZ, the health insurers association (ZN: Zorgverzekeraars Nederland), two persons from a consultancy agency and a professor with a special interest in health services research.
One of the consulted persons pointed out an important difference between medical devices and medicinal products. He claimed that, in contrast to medicinal products companies, no manufacturer of medical devices takes a disease as a starting point. Medical devices often constitute the last resort in a treatment process.
Another item to discuss with these experts was the prevalence threshold to define a product as an orphan. In Europe for orphan medicinal products this threshold is established at 50/100,000 inhabitants (see Table 2). This concerns 8,000 citizens in the Netherlands, which is considered by the CVZ and ZN to be a large group of people. This would mean that a lot of medical devices within the current standard

reimbursement package are orphan medical devices. The interviewed persons felt that for smaller target groups, a special arrangement would be advisable.
Universities sometimes account for a spin-off of small enterprises focusing on niche markets. Unfortunately, they often need to close down again, because the return on investments is too low. Potential investors look for profit and therefore they choose enterprises with the larger target groups. It is (theoretically) possible for small enterprises to join large companies, but in practice it is hard to convince the large companies of the opportunities. Aiming for larger patient groups seems the obvious thing to do for manufacturers, though sometimes, it can be expected that a device is only cost-effective for a smaller subgroup. This is important information for decision makers. The reimbursement status may not be reached because cost-effectiveness is not demonstrated for the broad indication group a manufacturer aims at. If there is no cost-effectiveness study available at all, which is often the case for medical devices, the decision makers' estimation of the budget impact may be too high and therefore the device might not be entitled for standard reimbursement.
One of the interviewed persons expressed the feeling that the market is globalizing, but that the different reimbursement systems hamper this development.

The consulted experts came up with three suggestions to stimulate the availability of medical devices for small target groups:

1. Provide for reimbursement of investigational medical devices. (Cost-) effectiveness may be proven in an experimental phase and the exact indication range could be established.
2. Develop a methodology for performing trials with small patient groups (e.g. with modelling).
3. Medical device manufacturers should bear in mind that if a medical device is not reimbursed by the government or health insurers, it is possible to sell the device at the private market. This might be the key to success for Dutch manufacturers, since it seems that in the Netherlands the disposable incomes of people are growing more and more. Still, a negative side-effect might be that only cheap products will be marketed.

5.2 Discussion

The ‘orphan problem’ in relation to medical devices appeared to be quite new to the persons consulted. Often, it was not easy for them to mention medical devices in relation to rare diseases. In a lot of cases the medical devices can be used for more than one (orphan) disease or condition. The ‘orphan problem’ in the world of medical devices seems to exist in certain treatments rather than in specific rare diseases. Considering the stages of the framework as formulated within this project it can be concluded:

1. **Planning and organization**
   Planning and organization seem to constitute serious problems to develop and market medical devices for small target groups. Small enterprises were mentioned by several interviewees as negative factors in the process of providing medical devices for small target groups.
2. **Research and development**
   The persons consulted expressed the difficulty to provide clinical effectiveness data. Cooperation between universities and companies, and research grants were mentioned as solutions.
3. **Regulatory pathway**
   Three manufacturers mentioned problems in the efforts to fulfil MDD requirements. Still, most manufacturers seem to have learned to comply with the essential requirements of the MDD. Some of the devices mentioned as orphans are custom made devices, for which a special arrangement is applicable in Europe.
4. **Reimbursement**
   All Dutch stakeholders named the reimbursement system as a major hurdle in marketing medical devices for small target groups. Some devices are not entitled for reimbursement or the standard tariff was not sufficient. (Cost-) effectiveness is hard to proof. An unclear picture of the budget impact of the introduction of a device in the standard insurance package might lead to the decision not to include the device in the package.

After sorting the suggestions made by the different stakeholders on how to stimulate the availability of medical devices for small target groups, four suggestions remained:

- The different stakeholders all pleaded for some sort of financial support for experimental products. This could be for developing the product and for investigating the effectiveness of orphan medical devices. Also reimbursement of investigational medical devices was mentioned several times. In this way the proof of (cost-) effectiveness for a defined indication range could be provided in an experimental phase.
- It was suggested that an independent organization should assess individual applications for reimbursement of a certain device. This assessment should be based on a decision model which is developed by a committee with representatives of all stakeholders. The assessment should result in a mandatory advice.
- The reimbursement authority should consider accepting less elaborate studies to support the (cost-) effectiveness in case of small target groups. Or a methodology for performing trials with small patient groups (e.g. with modelling) should be developed.
- Different stakeholders should cooperate closely together. A website or database for health care organisations, universities and companies with information on orphan products could provide a national picture of possibilities. People would know where to turn to with specific needs.

6 General discussion

This study yielded insights into orphan problems with medicinal products and especially with medical devices. Literature showed that the number of arrangements to support the development and availability of medical devices aiming at small target groups is lower than the arrangements for medicinal products aiming at small target groups.
Given the differences in the nature of medicinal products and devices (see paragraph 3.2) a mere transposition of the policies as used for orphan medicinal products is not evidently an appropriate way to foster the development and availability of orphan medical devices. This chapter will address the impediments and incentives per stage of a medical devices' lifecycle and an attempt is made to answer the question if the incentives within existing orphan programmes can work for European medical devices as well.

1. **Planning and organization**
   Planning and organization seem to constitute serious problems for developing and marketing medical devices for small target groups. This might be largely inherent in the nature of medical devices, since they are often produced by small entrepreneurial companies with all kinds of organizational problems. Especially for orphan medical devices it is very difficult to find unmet needs. And if a potential niche market is found, e.g. certain treatments for chronically ill and handicapped persons, the field might be very competitive.
   For small enterprises, a low return on investments, inherent in the orphan problem, is an additional problem which makes it difficult to survive. The existing orphan medicinal products programmes use market exclusivity as an incentive to improve the success rate for manufactures to sell. These measures are all based on normal patent protection. For unknown reasons, this incentive is not mentioned as an option for medical devices by the persons interviewed in this study. It needs to be investigated if this is a possible solution for European medical devices.
2. **Research and development (R&D)**
   The R&D stage contains several potential impediments for successfully reaching the market, especially for orphan products. Most of the investigated regions make use of incentives concerning cost reducing policies for R&D, like government grants for research on orphan products, tax credits and protocol assistance. From the interviews, it appeared that the provision of clinical effectiveness data is difficult for (orphan) medical devices. Cooperation between universities and companies, and research grants were mentioned as solutions.
3. **Regulatory pathway (general legal aspects, market approval and post marketing surveillance)**
   Within the regulatory pathway, all of the investigated regions make use of incentives aiming at reduction of application fees and expedited assessments. For medical devices, two special arrangements were found. In Europe, custom made devices are exempt from a review by a Notified Body. The USA legislation provides the possibility to gain an exemption from effectiveness requirements and assessments are given priority and may be shorter in practice. In Europe, most manufacturers seem to have learned to comply with the essential requirements of the MDD and the conformity assessment procedures.
4. **Reimbursement**
   Requisites for reimbursement of medical products differ from country to country, but generally speaking, outcome data and health economic evidence become more and more important for decision makers.
   In the USA there is an incentive in the R&D stage which has a negative influence at the

reimbursement stage, i.e. the Humanitarian Device Exemption may lead to such an unclear status (is the product investigational or approved?), that it becomes difficult to get a product reimbursed.
All Dutch stakeholders mentioned the reimbursement system as a major hurdle in marketing medical devices for small target groups. Some devices are not entitled for reimbursement or the standard tariff was not sufficient. (Cost-) effectiveness is hard to proof. An unclear picture of the budget impact of the introduction of a device in the standard insurance package might lead to the decision not to include the device in the package.
Only in the Netherlands, a reimbursement arrangement as an incentive for orphan medicinal products has been set up recently.

From the interviews it also became clear that in the Netherlands the distribution of the orphan problem over the four stages of the conceptual framework is different than found in the international literature. In the Netherlands, the orphan problem appears to focus more on R&D and reimbursement, while in the USA, the incentives are mainly focused on obtaining easier market approval, which means that in the USA the orphan problem is tackled in the R&D and regulatory affairs stage. A possible explanation is that there are considerable differences between the USA and Europe regarding procedures to gain market access and their appending costs. The costs are higher in the USA and the approval processes take longer than in Europe.

Before reading the conclusions and recommendations in this report, one should bear in mind that:

- It is written from a Dutch viewpoint. Other countries, even other EU member states, can have a different opinion.
- The need for orphan medical devices might be bigger than found in this study. One reason is that it is difficult to ask for something which is not available. Another reason is that umbrella organizations were asked. An in-depth study by consulting specific patient and clinician organizations is advisable.
- The impediments contributing to the existence of unmet needs may not be the same for each device. For example, the small market for a cardiovascular device may serve as the major disincentive to its development, whereas in another case, the need to submit clinical data to gain approval for a modification to a device may be the most significant deterrent to a manufacturer. Therefore, it’s necessary to find a better understanding of the links between unmet needs and the barriers to address them.

7 Conclusions and recommendations

7.1 Conclusions

In the Netherlands, the stakeholders experience impediments that hamper the availability of medical devices for small target groups. The major impediments are considered to be present in the planning & organisation stage, the R&D stage and the reimbursement stage within a medical device's life cycle. When manufacturers target at small patient groups, it is hard to provide clinical effectiveness data and even harder to provide cost-effectiveness data. Uncertainty about the budget impact of introducing a new medical device is likely to have a negative effect on reimbursement decisions.

Special programmes to support the development and marketing of products for rare diseases exist in the USA, Japan, Australia, Canada and the EU. These programmes aim at medicinal products and biologicals mainly. Only the USA and Japan have specific arrangements for medical devices as well. Existing incentives to foster the availability of medical products for small target groups are: market exclusivity, regulatory fee waivers, expedited assessments, exemptions from certain requirements, grants for research, tax credits, protocol assistance and reimbursement during an investigational period. Incentives suggested by different stakeholders are:

- Financial support for experimental products for developing the product and for investigating the effectiveness of orphan medical devices.
- Reimbursement of investigational medical devices to proof (cost-) effectiveness for a defined indication range in an experimental phase.
- Assessment of individual applications for reimbursement of a certain device by an independent organization, resulting in a binding advice.
- Acceptance of less elaborate studies to support the (cost-) effectiveness in case of small target groups by the reimbursement authority.
- Development of a methodology for performing trials with small patient groups (e.g. with modelling).
- Cooperation between different stakeholders through real or 'virtual' networks (a website or database) to provide a picture of possibilities for people with unmet needs.

To elaborate upon the feasible incentives for orphan medical devices, it is necessary to formulate a clear definition on orphan medical devices. Existing programmes for orphan products gave direction to elements to be considered:

- The prevalence of a specific target group:
  When the prevalence threshold of 50 per 100,000 citizens, as for orphan medicinal products in the European Union is used, the maximum market size for Dutch orphan medical devices would be about 8,000 persons. This was considered a rather large group. The USA probably felt the same way and lowered the threshold for orphan medical devices to 1.33 per 100,000 citizens, which would come down to about 220 persons for the Netherlands.
  In addition to that, it is advisable not to speak of rare diseases only, but of rare treatments as well. While the disease as such is not rare, the medical device may be beneficial for a limited number of patients.
- The 'impact on life':
  For orphan medicinal products a condition with a serious 'impact on life' is described as life-threatening, seriously debilitating or serious and chronic. This could be useful in the definition for orphan medical devices as well. Still, one should bear in mind that there are a lot of medical devices which are not life saving but mere assistive and improving the quality of life.

- Stimulation for marketing:
  Without incentives it is unlikely that the marketing of orphan medical devices will generate sufficient return to justify the necessary investment.
- Added value:
  No method of diagnosis or treatment of the condition in question exists, which has comparable efficacy and lower costs (in other words: the orphan medical device must have a clear added value over existing therapies or combination of therapies).
- Uniqueness:
  The device is unique; not a mere variant of an existing medical device or an extension of an existing range of medical devices.

7.2 Recommendations

The most important step to take away the experienced impediments hampering the availability of medical devices for small target groups is for the different stakeholders to interact.
For further exploration of unmet medical device needs, individual clinical specialists and patients should be consulted. Incentives for medical device manufacturers are necessary to address those needs. These incentives should mainly focus on the planning & organization of manufacturing, research & development and reimbursement. These focus points should be laid down in European arrangements as far as possible, but it can be expected that a European reimbursement system is not very realistic. Therefore specific national attention is needed as well.
It is recommended to organize a stakeholder meeting. These stakeholders should include representatives of medical device manufacturers, clinical specialists, patient organizations, research institutes, government, health care insurers and insurance funds. The aim of such a meeting should be twofold:

- To establish the definition of an orphan medical device, and
- To discuss the feasibility of existing and suggested incentives for orphan medical devices (both at a European and a national level).

The commitment of all stakeholders is required to foster the availability of medical devices for small target groups.

rivm

References

1 Definition derived from a proposal on priority medical devices. World Health Organization, 2006.

2 Definition derived from draft resolutions deferred from the fifty-ninth World Health Assembly and the 118th session of the Executive Board, 2006, EB 120/13.

3 Goodman, C., 2001.
An overview of public and private factors affecting medical device innovation. In: Innovation an Invention in Medical Devices, Workshop Summary. K.E. Hanna, F.J. manning, P. Bouxsein, and A. Pope (Eds.) Institute of Medicine. National Academy Press, Washington D.C. This free book is available at http://www.nap.edu

4 Siebert, M., Clauss, L.C., Carlisle, M., Casteels, B., De Jong, P., Kreuzer, M., Sanghera, S., Stokoe, G., Trueman, P., Wenk Lang, A., 2002, Health technology assessment for medical devices in Europe. Int. J. of Technology Assessment in Health Care 18: 3, 2002.

5 Jansen Kraemer H.M., 2001.
Introductory overview in: Innovation and Invention in Medical Devices, Workshop Summary. K.E. Hanna, F.J. manning, P. Bouxsein, and A. Pope (Eds.) Institute of Medicine. National Academy Press, Washington D.C.

6 Ramsey, S.D., Luce, B.R., Deyo, R., Franklin, G., 1998.
The limited state of technology assessment for medical devices: facing the issues. The American journal of Managed Care, September 25, Vol. 4, special issue, SP 188-SP199.

7 Black, N., Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996, 312: 1215-1218 (11 May).

8 Out, H.J., Broekmans, A.W., 2007. Wetenschappelijke business. Medisch Contact, nr. 24, pp 1024-1027.

9 Medical Devices Directive 93/42/EEC, Council Directive of 14 June, 1993.

10 Active Implantable Medical Devices Directive 90/385/EEC, Council Directive of 20 June, 1990.

11 In Vitro Diagnostic Medical Devices Directive 98/79/EEC, Council Directive of 27 October, 1998.

12 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal L 311, 28/11/2001 p. 67 – 128.

13 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance) Official Journal L 136 , 30/04/2004 P. 0001 – 0033

14 Scott, D.L., Alder, S., Usui, E., Lui, K., 2001. Orphan drug programs/policies in Australia, Japan, and Canada. Drug Information Journal, Vol. 35, pp. 1-16.

15 BIOTECanada Orphan Products Policy, April 2004. http://www.biotech.ca/media.php?mid=1119 (accessed April 2007).

16 http://www.fda.gov/orphan/index.htm (accessed February 2007).

17 21CFR 814 Subpart H: Humanitarian Use Devices.

18 U.S. Department of health and Human Services, Food and Drug Administration, Report to the Congress: Barriers to the availability of medical devices intended for the treatment or diagnosis of diseases and conditions that affect children, October 2004.

19 Regulation (EC) No 141/2000 of the European Parliament and of the Council of December 16, 1999 on Orphan Medicinal Products. Official Journal of the European Communities. Jan 22, 2000 (L18/1).

20 Regulation (EC) No 847/2000 of the European Parliament and of the Council of April 27, 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts similar medicinal product and clinical superiority. Official Journal of the European Communities. Apr 28, 2000 (L103/5).

21 Final COMP Report to the Commission in relation to Article 10 of regulation 141/2000 on orphan medicinal products, London, 25 July 2005. Doc. Ref. EMEA/35218/2005 .

22 Regulation (EC) No 1901/2006Commission of the European Communities. Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of the European Communities* L378 27/12/, 2006: 1–19.

23 Personal communication of one of the authors with mr. J. Bona of the FDA.

rivm

Annex I: Humanitarian Device Exemption Summaries of Safety and Possible Benefit

Date: 29th of October 2007

Device Name	Device Description/Device Indications
ENTERPRISE Vascular Reconstruction Device and Delivery System	Use with embolic coils for the treatment of wide-neck, intracranial, saccular or fusiform aneurysms arising from a parent vessel with a diameter of >= 3 mm and <= 4 mm. Wide-neck is defined as having a neck width >= 4mm or a dome-to-neck ratio < 2.
Onyx® Liquid Embolic System (Onyx® HD-500, Model 105-8101-500)	Treatment of intracranial, saccular, sidewall aneurysms that present with a wide neck (>= 4 mm) or with a dome-to-neck ratio < 2 that are not amenable to treatment with surgical clipping
Fujirebio Mesomark™ Assay	The Fujirebio Diagnostics, Inc. (FDI) MESOMARK™ is an Enzyme Linked Immunosorbent Assay (ELISA) for the quantitative measurement of Soluble Mesothelin Related Peptides (SMRP) in human serum. Measurement of SMRP may aid in the monitoring of patients diagnosed with epitheloid or biphasic mesothelioma. MESOMARK™ values must be interpreted in conjunction with all other available clinical laboratory data.
Abiocor® Implantable Replacement Heart	This device is indicated for use in severe biventricular end stage heart disease patients who are not cardiac transplant candidates and who • are less than 75 years old, • require multiple inotropic support, • are not treatable by LVAD destination therapy, and • are not weanable from biventricular support if on such support.
Karl Storz Semi-Rigid TTTS Fetoscopy Instrument Set, Karl Storz Rigid TTTS Fetoscopy Instrument Set with 0 or 12 degree scope, and Karl Storz Rigid TTTS Fetoscopy Instrument Set with 30 degree scope	The Karl Storz TTTS Fetoscopy Instruments Sets are indicated for selective laser photocoagulation (S-PLC) in the treatment of twin-to-twin transfusion syndrome (TTTS) for fetuses whose gestational age is between 16 and 26 weeks.
Wingspan Stent System with Gateway PTA Balloon Catheter	This device is indicated for improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with greater than or equal to 50% stenosis that are accessible to the system.
CoAxia NeuroFlo Catheter	This device is indicated for the treatment of cerebral ischemia resulting from symptomatic vasospasm following aneurismal subarachnoid hemorrhage, secured by either surgical or endovascular intervention for patients who have failed maximal medical management.
Vertical Expandable Prosthetic Titanium Rib (VEPTR)	For the treatment of Thoracic Insufficiency Syndrome (TIS) in skeletally immature patients. TIS is defined as the inability of the thorax to support normal respiration or lung growth. For the purpose of identifying potential TIS patients, the categories in which TIS patients fall are as follows: Flail Chest Syndrome Rib fusion and scoliosis Hypoplastic thorax syndrome, including • Jeune's syndrome • Achondroplasia • Jarcho-Levin syndrome • Ellis van Creveld syndrome
INTACS® Prescription Inserts for Keratoconus (0.25mm, 0.30mm, and 0.35mm)	INTACS® prescription inserts are intended for the reduction or elimination of myopia and astigmatism in patients with keratoconus, who are no longer able to achieve adequate vision with their contact lenses or spectacles, so that their functional vision may be restored and the need for a corneal transplant procedure may potentially be deferred. The specific subset of keratoconic patients proposed to be treated with INTACS® prescription inserts are those patients: • who have experienced a progressive deterioration in their vision, such that they can no longer achieve adequate functional vision on a daily basis with their contact lenses or spectacles;

Device Name	Device Description/Device Indications
	• who are 21 years of age or older; • who have clear central corneas; • who have a corneal thickness of 450 microns or greater at the proposed incision site; and • who have corneal transplantation as the only remaining option to improve their functional vision.
OP-1 Putty	For use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.
DeBakey VAD Child Left Ventricular Assist System	For use to provide temporary left side mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients (5-16 years old, with BSA>= 0.7 m^2 and <1.5 m^2) who are in NYHA Class IV end stage heart failure, are refractory to medical therapy and who are (listed) candidates for cardiac transplantation.
Heartsbreath	For use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The Heartsbreath test is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy. The use of the device is limited to patients who have had endomyocardial biopsy within the previous month.
CONTEGRA Pulmonary Valved Conduit	The CONTEGRA Pulmonary Valved Conduit is indicated for correction or reconstruction of the Right Ventricular Outflow Tract (RVOT) in patients aged less than 18 years with any of the following congenital heart malformations: • Pulmonary Stenosis • Tetralogy of Fallot • Truncus Arteriosus • Transposition with Ventricular Septal Defect (VSD) • Pulmonary Atresia In addition, the conduit is indicated for the replacement of previously implanted, but dysfunctional, pulmonary homografts or valved conduits.
Dermagraft	For use in the treatment of wounds associated with Dystrophic Epidermolysis Bullosa (EB).
Medtronic Activa Dystonia Therapy	For unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above
Neuroform Microdelivery Stent System	The Neuroform Microdelivery Stent System is intended for use with embolic coils for the treatment of wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter of greater than or equal to 2mm and less than or equal to 4.5mm that are not amenable to treatment with surgical clipping. Wide neck aneurysms are defined as having a neck of 4mm or a dome-to-neck ratio of <2.
NEUROLINK® System, including NEUROLINK® Stent & Delivery Catheter and NEUROLINK® Balloon Dilatation Catheter	The NEUROLINK® System is indicated for the treatment of patients with recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels ranging from 2.5 to 4.5 mm in diameter with > 50% stenosis and that are accessible to the stent system
Ascension® PIP	For use in arthroplasty of the proximal interphalangeal (PIP) joint when the patients has soft tissue and bone that can provide adequate stabilization and fixation under high demand loading conditions after reconstruction; and needs a revision of a failed PIP prostheis, or has pain, limited motion, or joint subluxation/dislocation secondary to damage or destruction of the articular cartilage.
VISX Excimer Laser System and Custom Contoured Ablation Pattern (C-CAP) Method™	For the treatment of asymmetrical ablation patterns from previous laser refractive surgery caused by decentration of the treatment as viewed on the Zeiss Humphrey® topography unit and treated with the STAR S3 ActiveTrak™ Excimer Laser System in patients: • who exhibit symptomatology supportive of visual defect: reduced best spectacle-corrected visual acuity, debilitating glare, monocular diplopia (double vision), and/or debilitating halos; and, • who pre-operatively have at least a 6 µm difference on the elevation topography, from

Device Name	Device Description/Device Indications
	the lowest point to the highest point, over a 6.5 mm diameter or over the patient's pupil diameter as measured by the Zeiss Humphrey topographer, whichever is larger
OP-1™ Implant	The device is indicated for use as an alternative to autograph in recalcitrant long bone nonunions where use of autograph is unfeasible and alternative treatments have failed.
Avanta Metacarpophalangeal (MCP) Joint Implant Finger Prosthesis	The device is indicated for use in arthroplasty of the MCP joint when either the: 1. patient is in need of a revision of failed MCP prosthesis(es); or 2. patient expects to place his/her hands under loading situations which preclude the use of an alternative implant in the painful osteo-arthritic and post traumatic MCP joint.
PROSTALAC Hip Temporary Prosthesis	This device is indicated for use as a short-term total hip replacement (THR) in patients who need a two-stage procedure to treat a confirmed infection of their THR and where vancomycin and tobramycin are the most appropriate antibiotics for treatment of the infection based on the susceptibility pattern of the infecting microorganism(s).
Composite Cultured Skin (CCS)	For use in patients with mitten hand deformities due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release of hand contractures (i.e., "mitten" hand deformities).
JOMED JOSTENT® Coronary Stent Graft	For Use in the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts > 2.75 mm in diameter.
TAS Ecarin Clotting Time Test	To be used to determine the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass in patients who have heparin induced thrombocytopenia (HIT).
Enterra™ Therapy System (formerly named Gastric Electrical Stimulation (GES) System	For the treatment of chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.
Telescopic Plate Spacer (TPS) Spinal System	To replace normal body structures following a vertebrectomy/corpectomy of the spine for metastatic disease in the cervical and/or cervico-thoracic spine (C3-T2). The TPS Spinal System implants are intended to correct spinal alignment and stablize the spinal operative site during fusion. TPS Spinal System implants attach to the spine anteriorly by means of their trapezoidal shape and by screws joined with a plate and spacer component.
TheraSphere®	For radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.
BioGlue®Surgical Adhesive	For use as an adjunct in the surgical repair of acute thoracic aortic dissections.
Shelhigh Pulmonic Valve Conduit Model NR-4000 with "No-React®" Treatment	For replacement of the diseased, damaged. or absent pulmonic artery in small children or infants up to age 4 years, with Transposition of the Great Arteries, Truncus Arteriosis, Tetrology of Fallot with associated cardiac anomalies or with Pulmonary Atresia, or replacement of failed conduits in young patients with accelerated conduit failure.
CardioSEAL®Septal Occlusion System	For the treatment of patients with complex ventricular septal defects (VSD) of a significant size to warrant closure, but that, based on location, cannot be closed with standard surgical transatrial or transarterial approaches.
Acticon™Neosphincter	For the treatment of severe fecal incontinence in post-pubescent males and females who have failed, or are not candidates for, less invasive forms of restorative therapy.
CardioSEAL® Septal Occlusion System	For the treatment of patients with complex single ventricle physiology who have undergone a fenestrated Fontan palliation procedure and require closure of the fenestration.
VOCARE® Bladder System	For the treatment of patients who have clinically complete spinal cord lesions (ASIA Classification) with intact parasympathetic innervation of the bladder and are skeletally mature and neurologically stable, to provide urination on demand and to reduce post-void residual volumes of urine. Secondary intended use is to aid in bowel evacuation
VOCARE® Bladder System	For the treatment of patients who have clinically complete spinal cord lesions (ASIA Classification) with intact parasympathetic innervation of the bladder and are skeletally mature and neurologically stable, to provide urination on demand and to reduce post-void residual volumes of urine.

Device Name	Device Description/Device Indications
Avanta Proximal Interphalangeal (PIP) Finger Prosthesis	For use in arthroplasty of the PIP joint when either the: (1) patient is in need of a revision of failed PIP prosthesis(es); or (2) patient expects to place his/her hands under loading situations which preclude the use of an alternative implant in the painful osteo-arthritic and post traumaic arthritic PIP joint.
Perma-Flow® Coronary Graft, Model 2C10	For single or multiple vessel coronary artery bypass in patients who are receiving coronary bypass grafting but who have inadequate autologous conduit to complete the required revascularization.
Excorim® Immunoadsorption System	For use in the treatment of patients with hemophhilia A and B who have Factor VIII or Factor IX inhibitor titers above 10 Bethesda Units/ml (BU/ml). The purpose of the system is to lower the inhibitor levels so that routine clotting factor rerplacement therapy can be considered. It may be used in an acute setting (to control bleeding during an acute hemmorrhage or for emergency surgery) or as a preventive measure to prepare patients for elective surgery.
Urostim	For use in children for the treatment of neurogenic bladder disease secondary to spina bifida
King's College Hospital (KCH) Fetal Bladder Drainage Catheter	For urinary tract decompression following the diagnosis of post-vesicular obstructive uropathy in fetuses 18 to 32 weeks gestational age
Harrison Fetal Bladder Stent Set (Lowery Modification)	For fetal urinary tract decompression following the diagnosis of fetal post-vesicular obstructive uropathy in fetuses of 18 to 32 weeks gestational age

Annex II: Consulted persons

Patients	
Council for Chronically ill and disabled persons (CG-raad: Chronisch Zieken en Gehandicaptenraad)	mr. Vreeswijk
Dutch Genetic Alliance (VSOP: Vereniging van Samenwerkende Ouder- en Patiëntenorganisaties)	ms. Evers
Care providers	
Dutch Association of Occupational Therapists (NVE: Nederlandse Vereniging voor Ergotherapie)	ms. Van der Biezen (secretariate)
University Medical Hospital of Groningen (UMCG: Universitair medisch Centrum Groningen)	mr. Postema (dept of Rehabilitation)
University Hospital of Amsterdam (AMC: Amsterdams Medisch Centrum)	mr. Jaspers
Medical device manufacturers	
Medtronic	ms. Eussen
Diagned	mr. Hes
Federation of Technology Branches (FHI)	mr. Knaven
Nefemed	mr. van Run
FME	ms. Verhagen - Wilcke
FARON	mr. van Pagée
Boston Scientific, Nederland	mr. van de Broek
Ness Nederland	mr. Rudolphie
Berkelbike	mr. Berkelmans
Stöpler	mr. Van Megen
Maastricht Instruments	mr. Lemmens
Others	
Dutch Branch organisation for Health Insurers (ZN: Zorgverzekeraars Nederland)	mr. Bakker
Dutch Health Insurance Board (CVZ: College voor zorgverzekeringen)	medical devices project team
Ministry of Health, Welfare and Sports (VWS: Ministerie van Volksgezondheid, Welzijn en Sport)	mr. Seeverens
University of Twente	mr. IJzerman
Seijgraaf Consultancy B.V.	mr. de Graaff
Medivinci	mr. Van Paassen
Food and Drug Adminstration (FDA)	mr. Bona