CAN A REGULATORY INSTRUMENT PROMOTE RESEARCH AND DEVELOPMENT INTO NEGLECTED DISEASES?

A POLICY DELPHI SURVEY

Doctoral Thesis

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by

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Abstract

Background

Rare diseases and neglected diseases are characterized by deficits in drug research and development (R&D) activities owing to market failures. Rare diseases do not offer a lucrative market because of the very small numbers of patients affected; neglected diseases, in contrast, are highly prevalent, but in poor and marginalized populations in developing countries. Public health policy responded to the R&D deficit for rare diseases with the adoption of orphan drug acts, i.e. regulatory instruments which contain financial and non-financial incentives for the pharmaceutical industry to encourage R&D into treatments for rare diseases. Similar legislation for neglected diseases does not exist, even though neglected diseases were part of the initial concepts which formed the basis for orphan drug acts. The debate about applying orphan drug acts to neglected diseases is ongoing in the scientific community. At the same time, a draft for an international medical R&D treaty has been developed, which proposes to restructure funding for medical research and development globally, and to heighten the role and financial obligations of the public sector, especially for neglected diseases.

Objectives

The prime objective of this research project was to gather stakeholders' opinions on the desirability and the feasibility of implementing a regulatory instrument to promote R&D into drugs for neglected diseases. Orphan drug regulations, the draft Medical Research and Development Treaty and their R&D-promoting mechanisms served as frames of reference. A secondary objective of this project was to explore the acceptance and the feasibility of the method of the Policy Delphi for our research question.

Methods

An international online-Delphi survey was conducted with stakeholders of different backgrounds and professional affiliations. Their opinions were compiled and

analyzed on causes for the treatment deficit for neglected diseases, on a possible definition of neglected diseases, on desirable and feasible measures to promote neglected disease R&D, and on the desirability and feasibility of a regulatory instrument to foster R&D for neglected diseases.

Results

117 (first round) and 56 (second round) stakeholders participated in the survey. In both rounds of survey, the majority of the respondents (88.4% first round, 86.8% second round) advocated the development of a regulatory instrument to promote R&D for neglected diseases. Most respondents (77.9% first round, 79.3% second round) also considered this to be a feasible option. With the exception of market exclusivity, which was viewed with skepticism, key provisions of orphan drug regulations were judged favorably also for neglected diseases. A majority (87.1 % first round, 77.2% second round) supported national funding obligations for neglected diseases which are proposed by the medical R&D Treaty.

Conclusions

While not all features of orphan drug regulations and of the draft Medical Research and Development Treaty received equal support, the view was expressed that a regulatory instrument would be a desirable and feasible measure to promote R&D for neglected diseases.

Declaration

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgment has been made in the text.

Cologne, June 18, 2012

Angela Fehr

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1 Introduction to the Research Project

"Although health is widely understood to be both a central goal and an important outcome of development, the importance of investing in health to promote economic development and poverty reduction has been much less appreciated."
(from the introductory remarks to the Final Report of the WHO Commission on Macroeconomics and Health; WHO, 2001)

According to the World Health Organization (WHO), more than one billion people worldwide suffer from so-called neglected diseases. (WHO, 2006f) Neglected diseases are mostly, but not exclusively, tropical infectious diseases, which affect poor and marginalized populations in the developing world. About 50% of the disease burden in developing countries can be attributed to poverty-related and neglected infectious diseases. (WHO, 2006e) Substandard living conditions and a lack of clean water and sanitary facilities contribute to the spread and persistence of neglected diseases. Neglected diseases, such as leishmaniasis or Buruli ulcer, cause immense suffering for the individual patient, and often lead to life-long disability. Their accumulated prevalence perpetuates a vicious cycle of poverty and disease, with long-lasting social and economic adverse effects on entire endemic regions. (WHO, 2010g) The persistence and the consequences of neglected diseases are an expression of what the WHO Commission on the Social Determinants of Health termed health inequities, that is "avoidable health inequalities" between groups of people within countries and between countries." (WHO, 2008, p. 1) Consequently, WHO not only speaks of neglected diseases, but also of "neglected communities"[3] (WHO, 2006d, p. iii)

The neglect of tropical infectious diseases encompasses the absence of treatments, insufficient medical research and development (R&D), and inadequate or no access to existing treatments. Poverty, equivalent to a lack of individual purchasing power and to financially ill-equipped health systems, is considered the root cause for the R&D deficit. For so-called tool-deficient neglected diseases, treatments are either completely lacking or inadequate, i.e. expensive, toxic, causing severe side effects,

[3] In its most recent report on neglected tropical diseases, WHO points out that it „may appear inappropriate" to speak of neglected diseases in the WHO context, as the organization „has never neglected them.". (WHO, 2010g, p. 7)

or requiring complex administration protocols that precludes their use in endemic regions. (Pécoul et al., 1999; Pécoul, 2004) Where treatments are available for neglected diseases, drug donation programs have brought temporary relief, yet these programs have not been sufficient in volume to reach all affected patient populations. (WHO, 2010g) Furthermore, lasting effects of existing controls are highly dependent on access to health care, and on reasonable standards of living in endemic countries. (WHO, 2006c)

This research project focuses on the R&D deficit for neglected diseases, and on two regulatory approaches to promote R&D into neglected diseases, i.e. orphan drug regulations and the draft Medical Research and Development Treaty (MRDT). Orphan drug regulations were created to stimulate drug development for rare diseases, i.e. diseases with very low prevalences in a given population. To this end, they contain incentives for the pharmaceutical industry, such as tax credits, grants, fee waivers and several years of market exclusivity for products developed for rare diseases. The first orphan drug regulation came into effect in 1983 in the United States, and was followed by similar legislation in Australia, Japan and Europe. (OrphaNet, 2010c) The success of orphan drug acts, and the perceived similarity of the structural R&D deficit between rare and neglected diseases, nourished a long-standing debate whether orphan drug incentives may also promote drug development for neglected diseases. While advocates for the application of orphan drug incentives to neglected diseases pointed to their success for rare diseases, skeptics referred to the prerequisite of an affluent market to serve their key incentive, i.e. market exclusivity. In the absence thereof, little benefit was expected from applying orphan drug laws to diseases of poverty. (cf. Bührlen et al., 2003; Milne et al., 2001; Trouiller et al., 1999; Villa et al., 2009)

A different regulatory approach to promoting R&D for neglected diseases was taken with the proposal for an international Medical Research and Development Treaty (CPTech, 2005b). Proceeding from the notion that current funding for medical R&D does not respond to public health needs, the authors and sponsors of this document propose national funding obligations for medical R&D, needs-based priority setting, and the separation of innovation incentives from drug prices to guarantee access to innovative products. The draft MRDT was presented to the WHO Commission on Intellectual Property, Innovation and Public Health (WHO-

CIPIH) in 2005 for evaluation (CPTech, 2005a; WHO, 2006e), and has been debated in follow-on WHO expert working groups up to the time of this writing. (WHO, 2010e; WHO, 2012g; WHO, 2008)

Against the background of current debates about regulatory approaches to correct the deficit in R&D funding for neglected diseases, we considered it timely, worthwhile and of relevant public health interest to explore, among stakeholders of various professional backgrounds and professional affiliations in developed, developing and threshold countries, the desirability and feasibility of creating and implementing a regulatory instrument to promote R&D into neglected diseases. Orphan drug regulations and the draft Medical Research and Development Treaty served as frames of reference for this project. To obtain quantifiable data, we performed a Policy Delphi survey, which follows the characteristic Delphi process of anonymous rounds of survey with feedbacks after each round, yet it does not aim to achieve consensus among the respondents. Instead, the objective of a Policy Delphi is to collect, explore and correlate views from a heterogeneous panel, and to present to political decision makers a range of options on which they may base their informed decision. (Linstone & Turoff 2002). Delphi surveys have long been applied to issues of health policy and health systems research. (cf. Daar et al., 2007; de Meyrick, 2003; de Villiers et al., 2005; Mullen, 2003; O'Loughlin & Kelly, 2004; Schopper et al., 2000) To the best of our knowledge, however, the method has not been employed to explore measures to promote R&D into neglected diseases. We designed and implemented the Policy Delphi as an international online exercise and pursued, as a secondary objective of this project, the aim to examine the acceptance and the feasibility of the method for our research question.

The concept for this research project was developed in 2005, at a time, when the debate on innovative financing mechanisms for neglected disease R&D gained considerable momentum at the level of WHO. These developments were both beneficial and challenging for us. They were beneficial, because they provided continuous input and reassurance of the public health relevance of our research topic. They were challenging, because at times they had the author question how relevant – in the face of intergovernmental working groups – a small project such as ours could be. This thesis cannot and will not strive to measure up to international commission reports. We had the privilege, however, of interesting more than 100

stakeholders in our two-round Delphi survey, who shared their knowledge and experience. The objective of a Policy Delphi, according to Turoff (2002), is to complement and to support decision-making processes of committee debates. We would be more than pleased if the outcome of this study could meet this objective.

This thesis document is divided into two parts. Part I introduces the issue of neglected tropical infectious diseases (Chapter 2 / Statement of the Problem) and gives an overview of orphan drug acts, the Medical Research and Development Treaty, and the possible application of these instruments to neglected diseases (Chapter 3 / State of the Art of Research). Part II presents the methods which were applied, and describes the design and implementation of the Policy Delphi survey (Chapter 4 / Methods). The results of the survey are reproduced in Chapter 5 (Results) and discussed in Chapter 6 (Discussion). The survey documentation as well as tabulations of frequency data and cross-tabulations are included in the Annex.

2 Neglected Diseases: A Global Public Health Challenge

The term 'neglected diseases' describes a heterogeneous (Aagaard-Hansen & Chaignat, 2010) group of predominantly, but not exclusively, tropical infectious diseases. As diseases of poverty, neglected diseases thrive in remote rural areas, urban slums or areas of conflict and unrest, where people are exposed to disease-transmitting vectors and lack sanitary installations, adequate supplies of fresh water[4] as well as access to health care services. (Liese et al., 2010; WHO, 2004a) Environmental risk factors, climate change, human-, livestock- and vector-migration, urbanization, gender and other socio-cultural factors further contribute to the prevalence and persistence of neglected diseases (Aagaard-Hansen & Chaignat, 2010). In the absence of a clear-cut definition, several disease-spanning features characterize neglected diseases. The WHO Commission on Macroeconomics and Health (CMH) ranked diseases from Type I to Type III, based on endemicity, burden of disease and pharmaceutical R&D activities. In this ranking, Type I diseases describe communicable and non-communicable diseases which are highly prevalent in both industrialized and in developing countries (e.g. measles, cardiovascular conditions, cancer, diabetes or smoking-related illnesses), and which are focused on by the pharmaceutical industry in its research and development efforts. Type II diseases include malaria, HIV / Aids and tuberculosis, prevalent in both developed and developing nations, but with a significantly higher prevalence in the latter. Type III diseases are tropical infectious diseases, prevalent nearly exclusively in developing nations, and lowest on the R&D agenda. Type II diseases are sometimes labeled 'neglected' and Type III 'very neglected' diseases (WHO, 2001, p. 78).

In 2001, the Médecins sans Frontiers (MSF) / Drugs for Neglected Diseases (DND) working group (Depoortere & Legros, 2001) selected parameters to describe the degree of neglect of tropical infectious diseases and collected data to establish a knowledge base aiming to enable the Drugs for Neglected Disease Initiative (DNDi) to select and prioritize research projects. (Ibid, p. 41) The parameters included, in short, the existence, the number and the quality of available treatments,

[4] In 2010, 783 million people globally relied on unimproved drinking water sources, and 2.5 billion people had no access to improved sanitation facilities. (http://www.who.int/research/en/, Accessed 6.4.2012)

diagnostic means or vaccines, the geographic distribution of the disease, prevalence and / or incidence rates, mortality / case fatality, and the burden of diseases measured by DALYs. Furthermore, R&D activities were assessed by determining the number of new chemical entities, ongoing clinical trials, the cost of treatment, and, *i.a.* the number of publications. (Ibid, p. 46 ff.) The working group concluded that "the answer basically can be reduced to an economical argument: Neglected diseases are those diseases whose treatments – in spite of the disease's magnitude and severity – do not have any market potential, and consequently do not promise a profitable financial return." (Ibid, p. 43), adding that "to define the concept of 'neglected diseases' is definitely a very complex exercise that has turned out to be rather philosophical at points." (Ibid, p.50)

In its recent First report on neglected tropical diseases, WHO named the following "common features of neglected tropical diseases":

- "[a] proxy for poverty and disadvantage
- [a]ffect populations with low visibility and little political voice
- [d]o not travel widely
- [c]ause stigma and discrimination, especially of girls and women
- [h]ave an important impact on morbidity and mortality
- [a]re relatively neglected by research
- [c]an be controlled, prevented and possibly eliminated using effective and feasible solutions." (WHO, 2010g, p. 5)

The groups of neglected diseases are not entirely homogenous and are further subdivided into tool-ready diseases, i.e. diseases for which treatments are available, and tool-deficient neglected diseases, for which no treatments are currently available. The WHO First report on neglected tropical diseases lists 17 neglected diseases (WHO, 2010g) while the Special Programme for Research and Training in Tropical Diseases (TDR)[5] covers 13 neglected diseases (WHO, 2004b), and the WHO Department of Control of Neglected Diseases lists 21, including neglected zoonotic diseases, as well as snakebite and podoconiosis. (WHO, 2006a). Four of

[5] TDR was established in 1975 and is funded by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO).

these 21 diseases are considered tool-deficient (Buruli ulcer, Chagas' disease, Human African Trypanosomiasis and Leishmaniases). The WHO Global Plan to Combat Neglected Diseases 2008-2015 includes 20 neglected diseases, acknowledging that the lists of diseases may differ between regional WHO offices. The Plan further subdivides tool-ready diseases into those targeted for elimination / eradication, and other tool-ready diseases, and distinguishes them from tool-deficient diseases; the latter group encompasses four neglected diseases, two neglected zoonotic diseases and two-vaccine-deficient viral infections (Dengue / Dengue Hemorrhagic Fever, Japanese encephalitis). (WHO, 2007) The U.S. Federal Food and Drug Administration Amendments Act of 2007 (FFDAAA) established priority review vouchers for sponsors of neglected disease products which apply to 16 tropical diseases (tuberculosis, malaria, blinding trachoma, Buruli ulcer, Cholera, dengue/dengue haemorrhagic fever, dracunculiasis (guinea-worm disease), fascioliasis, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis, soil transmitted helmithiasis, yaws), whereby the Act stipulates that the list may be extended to include "[…] [a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary." (United States Congress, 2007, p. 973) Table 2-1 below illustrates groups of neglected diseases within WHO.

Table 2-1 WHO: Tool-ready and tool-deficient neglected diseases

	WHO Department of Control of Neglected Diseases			WHO Global Plan to Combat NTDs			TDR	First WHO report on NTDs
	Tool-ready	Tool-deficient	Neglected zoonotic diseases	Tool-ready (targeted for elimination / eradication	Other tool-ready	Tool-deficient		
(Blinding) Trachoma	x				x			x
Anthrax			x			x		
Anthroponotic leishmaniasis					x			
Bovine tuberculosis			x					
Brucellosis			x			x		
Buruli Ulcer		x				x		x
Chagas' disease (American trypanosomiasis)		x				x	x	x
Cystercercosis	x		x		x			x
Dengue/ dengue hemorrhagic fever						x	x	x
Dracunculiasis (guinea-worm disease)	x			x				x
Echinococcosis			x		x			x
Endemic trepanematoses (yaws[7], syphilis, pinta)								x
Fascioliasis			x					
Foodborne trematode infections	x		x					x
Human African trypanosomiasis		x				x	x	x
Japanese encephalitis						x		
Leishmaniasis		x				x	x	x
Leprosy				x			x	x
Lymphatic filariasis	x			x			x	x
Malaria							x	
Onchocerciasis	x				x		x	x
Podoconiosis[6]								
Rabies			x		x			x
Schistosomiasis	x				x		x	x
Sexually transmitted infections							x	
Snakebite[6]								
Soil transmitted helminthiasis	x				x		x	x
TB/HIV coinfection							x	
Tuberculosis							x	
Yaws					x[7]			x[7]

Data Sources: WHO Department of Control of Neglected Diseases, http://www.who.int/neglected_diseases/diseases/en/. Accessed 3.8.2010; Special Programme for Research and Training in Tropical Diseases (TDR), http://apps.who.int/tdr/svc/diseases. Accessed 3.8.2010, First WHO report on neglected tropical diseases, 2010; WHO Global Plan to Combat Neglected Tropical Diseases 2008-2015 (WHO), http://whqlibdoc.who.int/hq/2007/WHO_CDS_NTD_2007.3_eng.pdf.)

[6] The WHO Department of Control of Neglected Diseases describes podoconiosis and snakebite as "other neglected conditions" (http://www.who.int/neglected_diseases/diseases/en/, Accessed August 7,2011)

[7] The WHO First Report on neglected tropical diseases includes yaws with the group of endemic trepanematoses.

As a result of efforts to eradicate tool-ready diseases, to develop treatments for tool-deficient diseases, and as a possible consequence of resistances being developed to existing treatments, the attributions may not be consistent over time.[8] To illustrate, leprosy and guinea-worm disease (dracunculiasis) are close to shedding the label of being neglected. Between 1985 and today, 14,5 million people were cured of leprosy; funding for leprosy is considered adequate and the disease is close to being eliminated, that is to reach a prevalence rate of less than one case in 10.000 people. Equally, the WHO Guinea-Worm Eradication Programme reduced the rate of infection from 3,5 million people in 20 endemic countries in the early 1980's to 10,000 cases in 9 countries in 2005. (WHO, 2006d)

At present, neglected diseases are endemic in 149 countries and territories, of which about two thirds report two or more and 30 report even six or more diseases. (WHO, 2006d) Together with maternal, perinatal and nutrition-related diseases, neglected diseases make up more than 50% of the burden of disease in low-income developing countries. (WHO, 2006e) 90% of the overall neglected disease burden is caused by blinding trachoma, Chagas' disease, leishmaniases, lymphatic filariasis, onchocerciasis, schistosomiasis and three soil-transmitted helminthes. (Hotez et al., 2009) However, the geographic concentration of neglected diseases in remote or marginalized areas of developing countries makes it difficult to gather reliable epidemiological data. (cf. WHO, 2004a) Furthermore, in most endemic countries, neglected diseases are not subject to compulsory reporting (Ehrenberg & Ault, 2005), and deficient (health) infrastructures and surveillance systems render little information on incidences, prevalences and mortality. Consequently, recent studies suggest that the prevalences for neglected diseases are possibly underestimated, which, when it comes to funding on the basis of burden of disease, would even magnify the extent of their neglect. (Vanderelst & Speybroeck, 2010; Aagaard-Hansen & Chaignat, 2010) Doubts have also been expressed on the validity of disease-adjusted life years (DALYs)[9] as proper measurements to reflect the burden

[8] Cf. a. Anderson (2009) who noted with reference to the list of tropical diseases included in the U.S. Federal Food and Drug Amendments Act of 2007 that: „In addition, the law has provided flexibility to add and remove diseases from the list based on new evidence. For example, a reason for updating the list on a periodic basis is that new products may become available and be proven effective against a particular neglected disease, at which point it may no longer be deemed necessary to provide incentives to spur innovation." (p. 1751)

[9] The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. http://www.who.int/mental_health/management/depression/daly/en/), Accessed 13.8.2011

of chronic neglected diseases, to describe their effect on the quality of life, and to serve as the basis for the allocation of funds. (Conteh et al., 2010; WHO, 2010g; Moran et al., 2009b). To illustrate, difficulties had been encountered in assigning proper disability weights that would adequately indicate (impaired) function. (WHO, 2010g)[10] Furthermore, co-morbidity may not have been sufficiently considered in the burden of neglected diseases. Patients suffering from neglected diseases are not only more susceptible to co-infections with HIV / Aids, malaria or tuberculosis (Molyneux et al., 2005); by the same token, morbidity from neglected diseases may have serious impacts on the progress and severity of other infectious diseases. (WHO, 2010g) Finally, morbidity from neglected diseases can be misattributed to other causes, and vice versa, owing to similar clinical symptoms or a lack of proper diagnostic tools. (Canning, 2006) As for mortality, neglected diseases had long been associated with low death rates, compared to HIV / Aids, malaria and tuberculosis; recent data now underline their high impact also on mortality in endemic countries. (WHO, 2010g)

Neglected diseases include bacterial, viral and parasitic infections, and show a variety of clinical symptoms, with often devastating long-term effects. Some diseases lead to lifelong disabilities which not only results in considerable work day losses in the adult population (Ehrenberg & Ault, 2005), especially in agrarian or rural societies (Ault, 2008), but which also stigmatizes patients, their families and social environment to the point of social marginalization and exclusion. (Ault, 2008). Especially soil-transmitted helminthes lead to school absenteeism and retarded growth and cognitive development in affected children. (WHO, 2004a) The economic burden caused by neglected diseases perpetuates a vicious cycle of disease and poverty for patients, families, communities and entire endemic regions (WHO, 2010d; Niens et al., 2010). Populations affected by neglected diseases are impoverished by the cost accruing for treatment; only 2.8 percent of the population in low-income countries, mostly in the upper segment of society, are covered by health insurance (United Nations MDG Gap Task Force, 2009). At a larger scale, neglected diseases thus contribute to a persistent global economic imbalance. (WHO, 2001) The lack of reliable data renders it difficult, however, to quantify the

[10] In 2007, a study, funded by the Bill&Melinda Gates Foundation, was initiated to update the Global Burden of Disease Study of 1990. Its results are due to be published in 2012. (http://www.globalburden.org/index.html)

true economic burden from neglected diseases. Additionally, it has been underlined that figures for economic impacts must not only consider quantifiable work day losses, but also take into account the vast burden of unpaid and unquantifiable work which is mostly carried out by women in endemic countries (WHO, 2010g) who make up 70% of the people living in absolute poverty. (Hampel, 2004) Any proper measurement of the impact of neglected diseases and of the return on investment for their control must therefore balance costs for prevention, treatment and loss of productivity against benefits in (agricultural) productivity, education and poverty reduction. (Conteh et al., 2010)

Geographical confinement to developing countries is a common feature of neglected tropical diseases; however, population mobility, including migration, travel, or child adoption, leads to a detection of cases in previously non-endemic regions. (WHO, 2010g) The U.S. Centers for Disease Control and Prevention consider Chagas' disease as a "Neglected Infection of Poverty in the United States" (www.cdc.gov/parasites/resources/pdf/nip_factsheet.pdf, Accessed 19.6.2011)[11] Overall, however, of the 133.000 deaths (0.2% of global deaths) attributed to six tropical diseases (trypanosomiasis, Chagas' disease, schistosomiasis, leishmaniasis, lymphatic filariasis and onchocerciasis) in 2008, only 25 occurred in developed nations. (WHO Health statistics and informatics Department, 2011)

Table 2-2 below gives an overview of the causes, prevalences, mortality, DALYs, clinical symptoms, long-term effects and economic impact of neglected diseases. Diseases in italic print are considered tool-deficient.

[11] In 2009, the first "National Summit on Neglected Infections of Poverty in the United States" was held. (Hotez et al., 2010) Currently, Chagas' is described as one of the „Neglected Parasitic Infections in the United States" (http://www.cdc.gov/parasites/npi.html, Accessed 26.05.2012)

Table 2-2 Causes, symptoms, prevalence and burden of neglected tropical diseases

(italics= tool-deficient diseases)

Disease	Cause	Incidence / Prevalence	Deaths in 2008	DALYs (000s) in 2004	Clinical symptoms	Long-term effects	Economic impact
Blinding Trachoma (incl. trichiasis)	*Bacterial infection (Chlamydia trachomatis)*	*approximately 84 people million are infected in 57 countries*	*81*	*1334*	*redness, watering, swelling, sensitivity to light, lumps in the eyelid, eye pain, corneal scarring, visual impairment*	*approx. eight million people are blind or visually impaired; leading infectious cause of blindness worldwide*	*2.9 billion U.S.$ p.a. lost productivity (8 billion incl. trichiasis)*
Buruli ulcer	*Bacterial infection (Mycobacterium ulcerans)*	*no global prevalence rates are available[12], the disease is endemic in approx. 33 countries; in 2010, 4.888 new cases were reported from 15 endemic countries*	*figures are available only on death owing to secondary causes(sepsis, tetanus)*		*formation of large ulcers, destruction of the skin*	*long-term functional disability if untreated*	*high economic burden on patient and health care system; treatment cost may range from 16-89% of a work year per household, depending on disease stage (Ghana 2001-2003) and are up to 7 times the average health spending per person (Australia)*
Chagas' disease	*Vector-borne parasitic infection*	*10 million infections in 2009, 35 million people at risk in 21 Latin American countries.*	*9.887*	*430*	*acute phase: mild symptoms, including fever, headache, lymph swelling, pallor, muscle / abdominal/chest pain, difficulties in breathing; chronic phase: cardiac (~30%) / digestive (~10%) disorders, neurological/mixed alterations*	*infection can lead to sudden death / heart failure*	*burden of medical care for all chronically ill patients equals appr. U.S.$ 267 per annum*

[12] WHO recorded various prevalence rates from endemic countries, ranging from 24.000 cases between 1978 and 2006 in Cote d'Ivoire to 144 cases in Australia between 2004 and 2006. The disease may be considerably underreported, since reporting BU is not compulsory in many countries. (WHO, 2012c)

Table 2-2 continued

Disease	Cause	Incidence / Prevalence	Deaths in 2008	DALYs (000s) in 2004	Clinical symptoms	Long-term effects	Economic impact
Dengue/Dengue Hemorrhagic Fever (DHF)	*Mosquito-borne viral infection*	*1 million confirmed cases annually, 50 million infections p.a., 2,5 billion people at risk, endemic in >100 countries*	*16.099*	*670*	*severe flu-like symptoms (DF); high fever, enlargement of the liver, poss. circulatory failure (DHF)*		*U.S.$ 587-1.800 million*
Guinea-worm disease (Dracunculiasis)	Parasitic infection transmitted via infested water	187 countries are disease-free or interrupted transmission; the annual incidence declined from 892.055 cases in 1989 to 1.797 in 2010			oedema, pruritus, ulceration, fever, secondary bacterial infections	temporary to permanent disability	
Human African Trypanosomiasis	*Vector-borne parasitic infection*	*endemic in 24 west and central African (90% of cases) and 13 east and south African countries(10% of cases), 55 million people are at risk, the estimated prevalence is between 50.000 and 70.000 patients; for the year 2009, 9.688 new cases of T.b. gambiense and 190 new cases of T.b. rhodendiense were reported*	*54.289*	*1673*	*first stage: fever, headaches, joint pains, itching; second stage: confusion, sensory disturbances, poor coordination, disturbance of sleep cycle, seizures, coma. 100% fatal if left untreated*	*Fatal if untreated*	*~U.S.$ 1.5 million per annum loss in income from agriculture*

Table 2-2 continued

Disease	Cause	Incidence / Prevalence	Deaths in 2008	DALYs (000s) in 2004	Clinical symptoms	Long-term effects	Economic impact
Leishmaniases: cutaneous (CL), mucocutaneous (MCL) and visceral forms (VL, also known as kala azar);	*Vector-borne parasitic infection*	*estimated prevalence of 12 million in 88 countries[13], 2 million infections p.a., 350 million threatened with infection*	*25.980*	*1974*	*CL: skin ulcers/ lesions/ scars,; MCL: partial or total destruction of mucous membrane,; VL: fever, weight loss, swelling of spleen and liver, anemia*	*CL / MCL and VL:. disabling, disfiguring; VL: fatal if untreated*	
Leprosy	Bacterial infection (Mycobacterium leprae), droplet-transmission	endemic in 122 countries, 213.000 infected, 244.797 cases were reported in 2009	11.716	194		permanent/progressive damage to skin, nerves, limbs and eyes if untreated	
Lymphatic Filariasis	Vector-borne parasitic infection	120 million infected, one billion at risk in 81 endemic countries	185	5941	fever, lymphoedema, enlargement of arms, legs, genitals, vulva and breast through lodging of worms in the human lymphatic system, kidney/lymphatic damage; asymptomatic forms are possible (no outward clinical symptoms, but internal organ affection);	second leading cause of disability worldwide, 40 million seriously incapacitated and disfigured	
Onchocerciasis	Vector-borne parasitic infection	~ 37 million people infected in 30 endemic countries	83	389		severe skin disease, visual impairment, and blindness; can shorten life expectancy in those infected by up to 15 years	

[13] Leishmaniases have to be reported in only 32 of 88 endemic countries. (WHO, 2010g, p. 22-23)

Table 2-2 continued

Disease	Cause	Incidence / Prevalence	Deaths in 2008	DALYs (000s) in 2004	Clinical symptoms	Long-term effects	Economic impact
Schistosomiasis (intestinal and urogenital form)	Parasitic infection (transmitted via infested water)	207 million people infected	44.057	1707	intestinal: abdominal pain, diarrhea, blood in the stool, liver/spleen enlargement; urogenital: haematuria, bladder/ureter fibrosis, kidney damage, bladder cancer, genital lesions, vaginal bleeding/pain, male infertility	20 million with severe consequences (disability weight of 0.5 probably underestimate)	
Soil-transmitted helminthiasis	parasitic infection	1 billion people infected	2.777 (ascariasis, trichuriasis, hookworm)		anaemia, nausea, tiredness, abdominal pain, appetite loss	school absenteeism, retarded cognitive development	

(*Data Sources*: (Niedrig et al., 2006; Aagaard-Hansen & Chaignat, 2010; WHO, 2010f; WHO, 2010c; WHO, 2010a; WHO, 2010b; WHO, 2010g; WHO, 2012c; WHO, 2012h; WHO, 2012b; WHO, 2012e; WHO, 2012d; WHO, 2012i; WHO, 2012f; WHO, 2012a)

In 2003, WHO launched a shift from vertical, disease-specific control efforts to population-based, disease-spanning approaches, which was laid down as a strategy in the Global Plan to combat neglected tropical diseases 2008-2015. (WHO, 2007) The shift took account of the multimorbidity and the geographical overlap that had been identified for neglected diseases in endemic countries, of the potential synergy effects of combining vertical disease-specific programs, and of the benefits expected from linking treatment delivery for neglected diseases with existing infrastructure for HIV / Aids, malaria and tuberculosis. (Hotez et al., 2006; Molyneux, 2004; Molyneux et al., 2005) For tool-ready diseases, preventive chemotherapy programs were launched and implemented as mass drug-administration; the drugs which are used[14] were considered safe enough to render a case-based diagnosis expendable in highly endemic regions. In addition to the safety and efficacy of the drugs used, benefits named for this strategy include the easy administration of drugs which does not require medically-trained staff. Furthermore, several drug donation programs by the pharmaceutical industry enable treatments free of charge. (WHO, 2010g, p. 22) Nearly 670 million people in 75 countries had been covered with preventive chemotherapy by the end of 2008. (Ibid, p. vii) The challenge remains, however, to secure sufficient quantities of treatments, and to deliver treatments to patients on the ground. Thus, the First WHO report concluded that targets for coverage cannot be met for some diseases which are eligible for preventive chemotherapy owing to a lack of donated drugs or insufficient drug production. (Ibid, p. ix)

Currently, WHO recommends five control strategies for tool-ready diseases, which are "(i) preventive chemotherapy; (ii) intensified case-management; (iii) vector control; (iv) provision of safe water, sanitation and hygiene; (v) veterinary public health." (Ibid, p. 21) In the absence of effective treatments for tool-deficient diseases, mechanisms to their control focus on early case detection, vector control, the improvement of environmental, sanitary and housing conditions, and the promotion of research and development into drugs and diagnostic tools. (Ibid, p. 25 ff.) Critics point to an imbalance of control strategies, which focus on biomedical, disease-specific approaches and neglect measures to improve national health

[14] Albendazole, mebendazole, diethylcarbamazine, ivermectin, praziquantel, levamisole and pyrantel are used in varying combinations depending on the indication for treatment. (WHO, 2010g)

systems and basic health care. (cf. Hein & Kickbusch, 2010) Thus, Spiegel et al. (2010) argue that the ratio between funds for biomedical research and interventions versus research and interventions on the social determinants of neglected diseases does not reflect the degree to which improvements in housing, sanitation and the environment contribute to reducing the burden of disease. This imbalance, so the authors claim, could be corrected if a certain percentage of all funds directed at innovations for neglected diseases would be earmarked "to address related socio-environmental and health system aspects." (Ibid, p. 1)

In 1990, the Commission on Health Research for Development calculated that only 5% of global health expenditure, which had amounted to U.S.$ 30 billion in 1986, was spent on health problems in low and middle income countries, in which 93% of preventable deaths occurred worldwide. The figure became known as the 10 / 90 gap (Global Forum for Health Research, 2010) and as a synonym for the neglect of diseases of poverty. It highlighted that drugs had become "ordinary commodities, subject to the laws and forces of a market economy." (Depoortere & Legros, 2001, p. 43) Between 1990 and 2001, global spending on health research increased from U.S.$30 billion to 105.9 billion (Dentico et al., 2005); still, in 1999, North America, Europe and Japan made up 82.4% of the global pharmaceutical market. (Trouiller et al., 2001) Table 2-3 below, taken from recent data of the G-Finder Reports[15], show current funding flows for tool-deficient Type III diseases in relation to Type II diseases.

[15] Against the background that funders of projects for Type II and Type III diseases lacked reliable information on funding needs and funding flows, the Bill and Melinda Gates Foundation supported a project to monitor funding flows. G-Finder Reports have been published annually since 2008 (http://www.policycures.org/publications.html.) Most recently, the data have also been made available in a publically accessible database. (https://g-finder.policycures.org/gfinder_report/)

Table 2-3 Funding for Type II diseases and for tool-deficient Type III diseases

		2007	2008	2009
Total Type II and Type III		2.560.068.749	2.955.964.344	3.178.605.592
HIV / Aids, malaria, tuberculosis	U.S.$	1.961.896.326	2.152.556.487	2.283.225.648
	% of total funding	**77%**	**73%**	**72%**
Chagas' disease	U.S.$	10.099.322	15.555.193	16.697.169
	% of total funding	**0.39%**	**0.53%**	**0.53%**
Leishmaniasis	U.S.$	51.270.622	57.742.199	69.384.940
	% of total funding	**2.00%**	**1.95%**	**2.18%**
Sleeping sickness	U.S.$	41.368.700	34.490.416	46.398.125
	% of total funding	**1.62%**	**1.17%**	**1.46%**
Buruli Ulcer	U.S.$	2.412.950	1.954.465	1.793.717
	% of total funding	**0.09%**	**0.07%**	**0.06%**

Data Sources: https://g-finder.policycures.org/gfinder_report/, Accessed 24.8.2011
Figures include funds for research, diagnostics, drugs, preventive/therapeutic vaccines, vector control/biologic products.

From the data which they have gathered, the authors of the G-Finder-Report analyzed that research funding and investment decisions for neglected diseases may not only be guided by science and epidemiology, but also by a presence of product development partnerships (PDPs) and civil society groups with active advocacy, fundraising and investment activities, by funders' perceptions and preferences, and by a presence of policy frameworks and funding mechanisms that prioritize specific diseases. (Moran et al., 2009c) Furthermore, given the lack of supportive structures for funders to identify projects and their funding needs, the Reports underline the need for better funding coordination to avoid duplication, to coordinate funding decisions among donors, and to direct investment towards tools with the highest health impact. (Moran et al., 2011)

Developing countries today are faced with increasing morbidity and mortality rates also from non-communicable diseases (Daar et al., 2007; WHO, 2010g) which marks a health transition towards a growing double burden of disease. (Hampel, 2004) Consequently, the focus laid on R&D efforts for Type I diseases by the private pharmaceutical sector is said to rightly reflect the low mortality rate of Type III diseases and the "convergence of patterns of mortality" (Stevens, 2004, p. 5) in both developed and developing countries. Stevens (2004) argues that for most Type

III neglected diseases there is no R&D or drug deficit, but an access deficit. (Ibid, p. 7) Therefore, "[…] in the future, low-income countries will derive significant benefit from drugs currently being researched with high-income country markets in mind. It would seem rather unjust, then, to vilify the pharmaceutical industry for spending research money on finding treatments for these areas; it is a simple case of the supply of research following the demand of mortality patterns […]." (Ibid, p.6)

Little public data is available on the exact costs for pharmaceutical research and development; figures relating to drug development differ considerably and range from approximately 115 million to 800 million U.S.$ (cf. DiMasi et al., 2003; Winters, 2006; Roche Pharmaceuticals, 2003) for a new drug to reach the market.[16] By the same token, "[e]stimates of future funding needs are necessarily inexact because of uncertainties about actual costs for each stage of research, attrition rates and the number of products entering development in a fast-moving scene." (WHO, 2006e, p. 75) Still, to be carried through to marketing approval, medical R&D programs must promise optimal return on investments (Webber & Kremer, 2001); a lack of purchasing power, i.e. market failure, disincentivizes medical R&D. (Hopkins et al., 2007; Herrling, 2007; Pécoul, 2004; Trouiller et al., 2001; Liese et al., 2010) Patent protection under the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (WTO-TRIPS, www.wto.org) is considered an essential incentive for the private sector to recover R&D investments. (Stevens, 2004) For neglected diseases in resource-poor settings, however, patents can both fail their incentive function (Winters, 2006) and block

[16] For an analysis of drug development cost s.a. BUKO Pharma, Pharma Brief, 3-4, 2011, available at www.bukopharma.de, and Médecins sans Frontières/Drugs for Neglected Diseases Working Group (MSF/DND) (Eds.): Tödliches Ungleichgewicht: Die Krise in Forschung und Entwicklung von Arzneimitteln gegen vernachlässigte Krankheiten., available at http://www.aerzte-ohne-grenzen.de/kennenlernen/veroeffentlichungen/dokumente-zum-herunterladen/publikationen-medikamentenkampagne/index.html

access to innovative products[17] (Médecins sans Frontières (MSF), 2007; Médecins sans Frontières (MSF), 2005). For reasons of market failure, Type III-neglected diseases have long been in the blind spot of pharmaceutical research and development. Webber and Kremer (2001) concluded that "[c]urrently, it is not financially feasible for private industry to match the level of research investment that is socially justified." (p. 736) The consequence for neglected diseases is that R&D programs are either not launched, or that they are discontinued after the discovery phase, before the clinical phase, at the development stage, or during the process of marketing application. If products for neglected diseases reach the stage of market approval, they are often too expensive for patients in developing countries, or ill-adapted to conditions on the ground. (Pécoul, 2004). As a result, of all drugs approved by the U.S. Federal Food and Drug Administration (FDA) between 1989 and 2000, less than 1% addressed diseases of poverty (Hubbard & Love, 2004); only 16 of 1393 new chemical entities marketed between 1975 and 1999 were for tropical diseases and tuberculosis, compared with 68,7% with "little or no therapeutic gain". (Trouiller et al., 2002, p. 2189) Trouiller et al. further analyzed that, despite considerable advances in understanding the pathophysiology

[17] The TRIPS Agreement of 1995 gives the owner of a (pharmaceutical) patent an exclusive 20-year right of making, using, offering for sale, selling, or importing a product or process. (WTO, 2003b; WTO, 2003a) During this time, the patent holder is protected from generic products and free in the pricing of the product. Developed countries had to translate TRIPS provisions into national law within one year of the Agreement's adoption; for developing countries, two deadlines were set (2000 and 2005), the longer period being granted to countries without prior legislation to protect foreign pharmaceutical patents. Least developed countries originally had to comply with TRIPS provisions by the year 2006; the deadline was extended to 2016 with the Doha Declaration to the TRIPS Agreement of 2001. Major controversies arose over the TRIPS Agreement and its impact on public health. Prior to the adoption of the Agreement, developing and threshold countries with functioning pharmaceutical industries, but without a legal structure to protect foreign pharmaceutical patents, had produced generic drugs for domestic markets as well as for countries which lacked R&D capacities and pharmaceutical patent legislation. Having become States Party to the TRIPS Agreement, they were then only allowed to produce generic versions of patented drugs if their governments either negotiated a voluntary license from the patent holder or, in case such license negotiation failed, issued a compulsory license (i.e. allow for the production of a patented product without consent of the patent owner). Compulsory licenses, however, only permitted the domestic use of the generic product. Severe consequences were anticipated from this ruling for least developed countries (LDCs), which had been beneficiaries and dependent on the import of cheap generic products. On August 30, 2003, a waiver was adopted for the obligation to produce generic products under compulsory licensing predominantly for domestic markets. At first glance, these Doha flexibilities, which now also allowed exports of generic products to LDCs, seemed to have averted the most serious public health consequences of the TRIPS Agreement. Several difficulties were identified, however, in its implementation. Firstly, the application of the compulsory license-ruling required complex administrative procedures for which least developed countries often lack the infrastructure or know-how. (Cohen-Kohler, 2007) Secondly, it became evident, that pressure was being exerted on developing countries to renounce their right to import drugs produced under compulsory licenses, and agree to so-called TRIPS+-provisions in bilateral trade agreements which eroded the original flexibilities. (Correa, 2006) As a consequence of the latter, the WHO Commission on Intellectual Property Rights, Innovation and Public Health called upon governments not to include in their bilateral or regional trade agreements any provisions that would counteract the flexibilities gained by the Doha Declaration. (WHO, 2006e) Another challenge arising from the Agreement concerned the limitation for threshold countries to export generic drugs only to LDCs. This ruling lead to low expected sales returns and difficulties with product development of generic drugs. In the end, market failure, again, threatened research and development efforts for diseases of poverty. (Luppe & Kreischer, 2004)

and molecular biology of some neglected diseases, between 1975 and 1999 the ratio between new chemical entities per million DALYs stood at 0.55 for infectious and parasitic diseases compared to 1.25 to 1.44 for diseases prevalent in developed countries. All drugs developed for neglected diseases in the given time, however, presented a clear benefit and were included in the WHO Essential Drug List. (Trouiller et al., 2002) These figures substantiated calls for an urgent shift from profit-oriented towards needs-based priority setting in health research and for "the enforcement of regulations and other mechanisms to stimulate essential drug development" as well as "[n]ew and creative strategies involving both the public and the private sector […]" (Trouiller et al., 2001, p. 945)

The 1990s had seen a growing awareness of the role which health played in safeguarding international security and stability, fostering economic development and reducing poverty and inequality. This awareness lead to a rising interest in global health issues. (Kickbusch, 2010a) It became apparent that there was an urgent need to step up public health efforts and to implement a strategy to promote R&D for neglected diseases. (WHO, 2006e) Three of the eight Millennium Development Goals targeted health issues (http://www.un.org/millenniumgoals/bkgd.shtml, Accessed 6.4.2012), and WHO commissions on Macroeconomics and Health, on Intellectual Property, Innovation and Public Health and on Social Determinants of Health provided ample data as well as policy recommendations to improve health, first and foremost for populations in developing countries. Thus, in the year 2000, the WHO Commission on Macroeconomics and Health, established to "assess the place of health in global economic development." provided "compelling evidence that better health for the world's poor is not only an important goal in its own right, but can act as a major catalyst for economic development and poverty reduction." (WHO, 2002, p. 1) In May 2003, with a view to identifying causes and solutions for the R&D deficit for neglected diseases, the World Health Assembly set up and tasked a Commission on Intellectual Property Rights, Innovation and Public Health (WHO-CIPIH) to "[…] collect data and proposals from the different actors involved and produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries…". (WHA, 2003, p. 2) The WHO-CIPIH concluded that a

"conjunction of positive conditions" for a self-sustaining cycle of medical innovation, including sufficient public funding for upstream research and a substantial market or the protection of intellectual property, was absent for neglected diseases. In developing countries, so the Final Report of April 2006 stated, there is little R&D funding and capacity both in the public and the private sector. On the demand side, markets are small and the health sector is underfunded. In developed countries, the private sector has little incentive to invest into R&D for neglected diseases, and publicly funded R&D also correlates with local disease burden. (WHO, 2006e, p. 171 ff.) Consequently, the WHO-CIPIH issued more than 50 recommendations, directed at national governments of developing and developed countries, at WHO and other international organizations, as well as at the private sector, encouraging them to promote public-health sensitive approaches to intellectual property rights, to step up R&D efforts for neglected diseases, develop and implement innovate funding schemes, invest in health infrastructure in endemic countries, increase pricing transparency, and reduce drug prices for developing countries. (WHO, 2006e) In 2006, an Intergovernmental Working Group was set up by the World Health Assembly, which, in May 2008, following a two-year process of international consultations, developed a "Global strategy and plan of action on public health, innovation and intellectual property". (WHO, 2008) This document included a further call to establish an Expert Working Group on Financing and Coordination (EWG), which, having been set up in 2009, evaluated 109 proposals on financing and allocation of funding for medical research and development, and presented its findings in a Final Report in 2010. In May 2010, a follow-on Consultative Expert Working Group (CEWG) was established which introduced its Final Report in April 2012. (WHO, 2012g) Also, in 2005, the European Parliament (EP) had adopted a comprehensive report on major and neglected diseases (European Parliament, 2005), advocating an expansion of the European and Developing Countries Clinical Trials Partnership (EDCTP) program beyond HIV / Aids, malaria and tuberculosis to include neglected diseases. The Report further supported an inclusion of neglected diseases in any activities of translational research planned for the European Union's Seventh Research Framework Programme and called "[…] for collaboration with the pharmaceutical industry on poverty diseases, with a new framework proposal for R&D in such diseases, to provide incentives for investment, including protocol assistance, fee waivers, tax

credits, subsidies, innovation prizes, assistance for prequalification, advance purchase commitments and partial transfer of patent rights to drugs;" (European Parliament, 2005, p. 11)

Numerous international or regional organizations, governments, private sector companies, foundations and humanitarian organizations[18] launched or supported measures which aimed to improve local health infrastructure in developing countries, strengthen local research capacities, promote technology transfer, prevent brain-drain from developing countries, consider a public health-sensitive implementation of international patent regulations and create incentives and public private partnerships to encourage drug research and development. These multifaceted efforts were flanked by debates on priority setting and health economics (cf. Berndt et al., 2007; Webber & Kremer, 2001; Canning, 2006), on health and human rights (cf. BMZ, 2009; Robinson, 2007; Hunt, 2007; WHO, 2006b; Razum et al., 2006; Pogge, 2005; WHO, 2005) and on ethics. (cf. Chokshi, 2008; Coleman et al., 2008; Jayasinghe et al., 1998; Krebs, 2008; Pakes, 2006; Stefanini A, 1999; Cohen-Kohler, 2007) Success was indeed made in reducing the burden of some tool-ready neglected diseases (WHO, 2006d; WHO, 2010g). Furthermore, while up until the end of the last millennium the pipeline for drugs for neglected diseases had been nearly empty, Moran et al. (2005) identified dramatic changes for the better from the year 2000 onward, owing to the formation of public private partnerships (PPP). Having analyzed neglected disease R&D from 1975 to 2004, the authors found that there were not only 63 products[19] under development by PPPs by the end of 2004, but that these products were being developed at a fraction of the usually calculated costs for drug development. (Ibid, p. 12) Multinational companies, so the authors found, were motivated to engage in R&D for neglected diseases not for commercial reasons, but for reasons of corporate social responsibility, for reasons of "minimising reputational risk stemming from failure to address developing country needs" and for strategic reasons, *i.a.* "positioning themselves in emerging developing country markets […];…"." (Ibid,

[18] Cf. e.g. the WHO „Summary of landmarks in overcoming neglected tropical diseases" in the First WHO report on neglected tropical diseases (2010), p. 9, available at http://whqlibdoc.who.int/publications/2010/9789241564090_eng.pdf

[19] Of these, five were for Human African Trypanosomiasis, two for Chagas' disease, three for Dengue, three for visceral leishmaniasis and one for onchocerciasis. The remaining drugs are for malaria and tuberculosis. (Ibid, p. 19 ff.)

p.11) Against the background of changed responsibilities and motivations, the authors warned that policy recommendations that called for commercial incentives for the private sector to stimulate R&D into neglected diseases, misjudged the current situation and might even "shift current company activity from a strategic/altruistic approach to a for-profit model, at an additional and probably unsustainable cost to the public purse of many billions across all neglected disease products." (Ibid, p. 17) However, while public private partnerships were seen as providing "[m]aximum health outcomes for developing country neglected disease patients", they were also threatened by „low sustainability" owing to their reliance on public or philanthropic funding. (Ibid, p. 65)

The number of actors in the field of global health grew exponentially in the past two decades, yet the health situation of the poorest populations has not improved significantly. Philanthropy increased funding for diseases of poverty, but also produced imbalances when well-funded philanthropic programs cause an internal braindrain to the detriment of financially less well-equipped local health systems. Thus, WHO leadership was called upon to coordinate global health actors and activities and to ensure needs-based priority setting, transparency and accountability. (cf. Kickbusch, 2010a)

3 A Regulatory Instrument to Promote R&D into Drugs for Neglected Diseases: Perspectives on Two Options

3.1 Option 1: Orphan Drug Regulations - R&D Incentives for Rare Diseases

There is a long-standing debate about adequate mechanisms to promote R&D into neglected diseases, taking into account the absence of viable markets in developing countries.[20] One such option which has been considered is the application of orphan drug regulations to neglected diseases. Orphan drug regulations were developed to create incentives for the pharmaceutical industry to develop treatments for rare diseases. The rationale behind orphan drug regulations was that, without reducing the costs of research and development, and without financial incentives, little to no research into the development of treatments for rare diseases would be undertaken. (European Parliament and European Council, 2000; United States Congress, 1983) Occasionally, neglected diseases and rare diseases are grouped under the term "orphan diseases" in an attempt to make clear that both groups of diseases have been 'orphaned' by the pharmaceutical industry in terms of drug research and development. (Hogerzeil, 2005) A clear distinction has to be made, however, between this comprehensive use of the term 'orphan diseases', and the term 'orphan drugs', which exclusively describes drugs for rare diseases. (EURORDIS, 2009) The following paragraphs will give an overview of the topic of rare diseases, of the history of orphan drug acts, and of their current application, successes and deficits.

Rare diseases are a heterogeneous group of diseases which span all medical disciplines. (cf. www.orpha.net) Between 5.000 and 8.000 rare diseases are known today, eighty percent of which are genetic diseases. The majority of the known rare diseases are chronic, severe or even life-threatening.[21] (Wetterauer & Schuster, 2008) There are no globally applicable prevalence or incidence limits for rare

[20] Cf. Trouiller et al. (2002), who highlighted that in OECD countries, annual public spending for drugs amount to $ 239 per capita, compared to less than $ 20 per year per capita in most developed countries on all health programs, and less than $ 6 in sub-Saharan Africa, including drugs. (p. 2191)

[21] To receive orphan drug designation for a medicinal product under the European orphan drug regulation, a disease has to be a „[…] life-threatening or chronically debilitating condition affecting nor more than five in 10 thousand persons in the Community […]"(European Parliament and European Council, 2000)

diseases. Instead, national or regional orphan drug acts[22] determine what constitutes a "rare" disease. Patient numbers for each rare disease are low, the total population of patients afflicted with them, however, is not. (Table 3-1)

Table 3-1 Rare disease prevalence limits and estimates

Rare Disease Prevalence Limit (in 10.000 people)				**Rare disease prevalence estimates**	
U.S.	EU	Japan	Australia	U.S.: N (% of total population)	EU: N (% of total population)
7 / 10.000	5 / 10.000	4 / 10.000	1.1 / 10.000	25 million (approx. 8.4%)+	13.5 to 25 million (3-6%)*
					27 to 36 million (6-8%)**

*+(Knight & Senior, 2006), *(Aymé & Schmidtke, 2007; Wetterauer & Schuster, 2008) **(EMA, 2011)*

Rare diseases bring particular hardships upon patients, on top of the severity and chronicity of the disease. In a survey conducted in 2005 among 5.980 patients, the European Organisation for Rare Diseases (EURORDIS) found that 40% of the respondents had been misdiagnosed at disease onset, and 25% had waited between five and 30 years for a correct diagnosis; 33% of the survey participants had received inappropriate medication, and 16% had undergone inappropriate surgery. (Knight & Senior, 2006; EURORDIS, 2009) For the vast majority of the known rare diseases, scientific knowledge about the causes are still lacking. (EMA, 2011) Medical experts, as well as patients, are few and geographically dispersed, and special coordinative efforts, sometimes across national borders, are necessary to conduct multi-center or multinational clinical trials. For many rare diseases, valid diagnostic procedures and therapeutic guidelines are lacking, and available treatments often only alleviate the symptoms, but cannot cure the disease. The heterogeneity of rare diseases had long overshadowed 'rarity' as a common denominator and as a cause for unique infrastructural problems. (Aymé & Schmidtke, 2007; Wetterauer & Schuster, 2008) The small number of patients equals a small market for the pharmaceutical industry and, in view of the high

[22] Over the past decades, legislation on orphan drugs has been implemented in the United States (1983), Singapore (1991), Japan (1997), Australia (1998) and the European Union (2000). An overview of orphan drug regulations worldwide is available at http://www.orpha.net. The Singapore "Orphan Drugs Exemption" does not contain epidemiological criteria for rare diseases and defines them as life threatening and severely debilitating; it further differs from the other orphan instruments in that it does not provide for financial incentives or market exclusivity, but only serves to regulate the import of drugs for rare diseases to Singapore. (OrphaNet, 2010a)

development costs for drugs,[23] rare diseases offer little investment incentive. (Denis et al., 2009)

The orphaning of drug development for rare diseases is traced back to 1962, when, following the thalidomide tragedy, the Kefauver-Harris amendments to the U.S. Federal Food, Drug and Cosmetic Act were passed which required that controlled studies be performed for all drugs to prove that they are safe and effective.[24] Costs of drug development rose, and as a result, the pharmaceutical industry orphaned drugs for small patient populations for the sake of research and development into more common diseases. (Haffner et al., 2002) Even where treatment options for a rare disease were discovered during research into a more common disease, it was rarely possible to find sponsors to pick up the findings and carry the research through to clinical trials, product development and marketing approval (Haffner, 1991). To aggravate, if the data were part of published research, they were no longer eligible for patenting, and there was no further perspective for return on investment. (Rogoyski, 2006) In the 1970s, however, as a consequence of the lack of a public health strategy to promote R&D for rare diseases, patients and their families in the United States joined forces, demanded a right to equal medical attention and treatment, and called for political action. (National Organization for Rare Disorders, 2007) Their commitment contributed to the adoption of the first orphan drug regulation, the U.S. Orphan Drug Act of 1983. An Interagency Task Force on Significant Drugs of Limited Commercial Value (Interagency Task Force to the Secretary of Health, 1979) was convened by the Bureau of Drugs of the Food and Drug Administration and charged with the task "to propose a policy, action and means to meet the recognized problem of inadequate source and motivation for development and distribution of useful drugs deemed to have little or no commercial interest." (Ibid, p. 4) The Task Force clearly acknowledged the role played by "health consumer activism" (Ibid, p. 5) in pushing government action towards incentives for rare disease research and development. For about a decade,

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[23] Figures on drug development costs are controversial and range from approximately 110 million (cf. Médecins sans Frontières (MSF) & Drugs for Neglected Diseases Initiative, 2001) to 800 million U.S.$ (DiMasi et al., 2003; Roche Pharmaceuticals, 2003) for a new drug to reach the market. The process can take between two to four years for the screening and discovery phase, and another eight to nine years for the clinical testing phase. (Trouiller et al., 1999)

[24] Cf. a. http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/default.htm

the Task Force performed research into different options[25], including surveys among stakeholders, before the United States Congress adopted the Orphan Drug Act (ODA), which would become a blueprint for similar legislation in Australia, Japan and the European Union.[26] The objective of the ODA was to encourage the pharmaceutical industry to step up R&D for rare diseases. To this end, it offered incentives that would support the process at different stages, i.e. grant programs, assistance in the design of protocols for clinical trials, tax credits for qualified clinical testing, fee waivers for regulatory application processes, and a seven-year market exclusivity for orphan products upon marketing approval.[27] (Haffner, 1991) A "principle of integrity" (Interagency Task Force to the Secretary of Health, 1979, p. 2) was to be observed, ensuring that the incentives granted must not compromise the safety or effectiveness of a rare disease treatment.

Following its adoption in 1983, the U.S. Orphan Drug Act was amended in 1984, 1985 and in 1988. The first amendment of 1984 defined epidemiological criteria, stipulating that orphan drug designation would be awarded to products that target diseases which affect less than 200,000 persons in the U.S. [28], and to those which affect more than 200,000 persons in the U.S., but for which there is no reasonable expectation that the U.S. sales will recoup the investment. (Haffner, 1991) Prior to

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[25] In 1974, the U.S. Food and Drug Administration established an Interagency Committee on Drugs of Limited Commercial Value, which, in its 1975 Interim Report, called for more detailed investigations into the issue of rare disease research and development deficits. The Interim Report was followed by a report on the Control of Huntington's Disease, by government appeals to the Pharmaceutical Manufacturers Associations, and by the creation of a Task Force in 1978, whose concluding report in 1979 became „the basic legislative and regulatory approach and provisions for orphan product development". (Haffner, 1991, p. 606)

[26] The U.S. Orphan Drug Act (ODA) of 1983 amended the Federal Food, Drug and Cosmetic Act through the establishment of an orphan drug designation and of incentives measures, the Public Health Service Act through the creation of an Orphan Products Board, and the U.S. internal revenue code through tax credits for qualified clinical testing expenses. Additionally, it "provided authority for the FDA Orphan Products Grants Program" to make grants for qualified clinical testing expenses. (Department of Health and Human Services - Office of Inspector General, 2001; United States Congress, 1983)

[27] Market exclusivity for an orphan drug only refers to the orphan indication for which marketing approval has been sought. The same drug may be approved for marketing within the seven-year period if the application is for another indication. Conversely, another drug for the same orphan indication may be approved for marketing within the seven-year period if the first sponsor is unable to provide sufficient quantities of the drug, if he consents to the approval of another application or if another drug proves clinically superior to the drug which was approved first. (Department of Health and Human Services - Office of Inspector General, 2001)

[28] The prevalence limit for rare diseases in the United States initially was an "arbitrary ceiling based on the estimated prevalence of narcolepsy and multiple sclerosis." (Department of Health and Human Services - Office of Inspector General, 2001)

this amendment, a medicinal product had been awarded orphan drug designation[29] if it occurred "so infrequently in the United States" (United States Congress, 1984) that a lack of economic viability would otherwise have hampered, or precluded, its development. Owing to this demand for proof of lack of economic viability, the pharmaceutical industry had been hesitant to submit applications for orphan drug designations during the first year of the Act's enforcement. (Leis García, 2004) The second Amendment, adopted in 1985, established access to a Federal Grant Program; furthermore, it extended the market exclusivity privilege to patented and patentable orphan drugs. (United States Congress, 1985) Previously, only unpatented or unpatentable drugs had been awarded market exclusivity under the Orphan Drug Act; the United States Congress had been convinced that patents would provide sufficient incentive for an investment into rare disease treatments. (Leis García, 2004) The 1985 Amendment took account of the fact that, while it had been easy to identify unpatented drugs, it seemed difficult to assess a drug's patentability. (Rogoyski, 2006, p. 5) The 1988 Amendment, eventually, established that a request for orphan drug designation must be filed prior to the submission of an application for marketing approval; originally, such request could be filed anytime before marketing approval. (Haffner, 1991; United States Congress, 1988) This ruling, however, only applies to the unapproved orphan use of a drug; the drug may have been approved for other indications already. (Seoane-Vazquez et al., 2008) From its adoption in 1983 to the year 2009, 2002 applications for orphan drug designation were approved, and 352 drugs to treat rare diseases received marketing authorization in the United States. (Wellman-Labadie & Zhou, 2009) To compare, in the ten years before the passing of the Orphan Drug Act, only ten orphan drugs had been approved for marketing. (Grabowski, 2005) Against the background of these figures, the U.S. Orphan Drug Act and the choice of its incentives have been described as a "tremendous success" (Leis García, 2004, p. 1) and even "the most successful US legislative actions in recent history" (Haffner et al., 2002, p. 821). Initial appropriations for rare disease research were $ 500,000 per annum for the first year of the ODA's implementation in 1983 (Haffner et al.,

[29] To benefit from incentives under the ODA, a sponsor has to file an application for orphan drug designation of a medicinal product with the FDA Office of Orphan Products Development. The application has to contain "details on the rare disease for which the drug will be investigated, the specific indication for the drug, a description of the drug, documentation of disease prevalence, and the regulatory and marketing status and history of the product." (Department of Health and Human Services - Office of Inspector General, 2001)

2002). The amount rose to currently $ 30 million per annum for the fiscal years 2008 through 2012. (United States Congress, 2007)

In the course of the ODA's implementation, it has been questioned, however, whether the increase in orphan drug development was truly the result of ODA incentives, particularly of market exclusivity.[30] In fact, studies on the performance of orphan drug acts indicated that the role of market exclusivity as an incentive may have been overestimated (Rogoyski, 2006; Seoane-Vazquez et al., 2008) The Department of Health and Human Services (DHHS) report on the ODA's impact found that "The lack of exclusivity, however, does not prevent companies from entering the market through conventional means.". (Department of Health and Human Services - Office of Inspector General, 2001, p. 8) Orphan product development may also have increased as a result of developments in patent law[31] and of the growth of the pharmaceutical and biotech industry in the early 1980s. (Rogoyski, 2006) Likewise, the very incentives of the Orphan Drug Act may have triggered the rapid increase of the biopharmaceutical industry, since the perspective of monopoly profits through market exclusivity enabled these firms to attract venture capital. (Leis García, 2004) Moreover, since the adoption of the ODA Amendment of 1985, orphan drugs could be patented or patentable products; some orphan drugs even hold a patent life which extends beyond a seven year-market exclusivity. The considerable number of patented drugs with additional market

[30] In its report on the impact of the Orphan Drug Act, the Office of Inspector General judged that "Other incentives, including tax credits and the waiver of user fees, are not nearly as critical as the prospect of marketing exclusivity, which is especially important to small companies trying to raise public and private capital." (Department of Health and Human Services - Office of Inspector General, 2001, p. 8)

[31] Rogoyski (2006) argues that a Supreme Court ruling in the early 1980s, which allowed the patenting of engineered bacteria and thus "set the stage for the development of the biopharmaceutical industry" (Ibid. p.17), as well as the creation of a Court of Appeals for the Federal Circuit in 1982, which "immediately took a pro-patent stance" (Ibid. p.17) had been "omitted from the Official Story" (Ibid. p. 16) of the increase in orphan product development. Such increase would further mirror the growth of the pharmaceutical and the biotech industry, which, between 1980 and 2003, increased its R&D spending from 2 billion to 33 billion U.S.$. Additionally, patent life was extended following the Hatch-Waxman Act of 1984 (extension of patent terms for up to five years to compensate the sponsor for time lost during marketing approval time) and through the Prescription Drug User Fees Act (PDUFA) of 1992 (sponsors had to pay FDA user fees for marketing approval which the FDA invested in the number of reviewers to speed up the approval process) The average time between application and approval for marketing authorization thus decreased from 30 to 18 months and the current average patent life for an approved drug ranges between 11 and 12 years. (Ibid. p. 18)

exclusivity[32] cast doubts on the sole effect of this ODA incentive as the chief driving force behind rare disease R&D. It lead to the hypothesis that the ODA and its market exclusivity incentive may have been "superfluous this whole time" (Rogoyski, 2006, p. 21), and only served a minority of "developers of unpatentable drugs, and drugs for which patent protection will expire within seven years of approval. For the patented remainder, the ODA […] has theoretical value as a form of insurance." (Ibid. p. 22), for instance in the case of patent litigations.

Apart from being questioned as the sole driving force for orphan product development in the U.S., market exclusivity has been criticized as a method to "privatize something that is in the public domain, such an [sic!] invention paid for by tax dollars, or a patent that has expired." (Love, 1999). And even though in passing the Orphan Drug Act, "Congress concluded that the benefits of access to new treatment outweighed the costs of granting a monopoly […]." (Department of Health and Human Services - Office of Inspector General, 2001, p. 10), rising costs for medical care, unaffordable orphan drugs and abuses of the ODA incentives triggered calls for the Act's reform. (Thoene, 1991) Several attempts were made to correct what was perceived as public health deficits in the Orphan Drug Act. The U.S. House Resolution (H.R.) 4638 (1990) proposed that orphan drug designations shall not only be awarded on the basis of prevalence data at the time of the request, but also "on the basis of projections as to the number of persons who will be affected by the disease or condition 3 years from the date the request for designation of the drug is made […]."(Rep Waxman, 1990) The objective was to limit the number of "expanding orphan diseases", i.e. diseases which surpass the prevalence limit for rare diseases within the period of market exclusivity. (Pulsinelli, 1999 p. 323, as quoted in Leis García, 2004, p. 20) Additionally, H.R. 4638 aimed to open the market for other sponsors if, during the period of market exclusivity, prevalence criteria for a rare disease were no longer met. This would have amended the provision of the Orphan Drug Act of 1983 which stipulates that other drugs for the same indication can only be approved for marketing if the sponsor was unable to

[32] Rogoyski (2006) found that 41% of the orphan drugs approved between 2001 and 2003 were unpatented or had a patent term which was due to expire before the onset of the seven year-market exclusivity; 28% were unpatented or had a patent term which would expire within the seven year-market exclusivity; 79% of the approved orphan drugs had patent protection, for 72% of these, patent protection extended beyond the seven year-market exclusivity. The author concluded that the "true engine of orphan drug development has been the patent system" and that the "ODA may not be the dominant incentive for orphan drugs". (Ibid. p. 21)

provide sufficient quantities of the drug or if he consented to the approval of additional licenses. The draft amendment also proposed to allow shared market exclusivity in cases in which it was found that drugs for a rare disease had been developed simultaneously.[33] (Rep Waxman, 1990) Orphan drug sponsors' criticized this proposal, arguing that the prospect of having to share market exclusivity would "disturb initial financial risk assessment". (Leis García, 2004, p. 21) In 1992 and 1994, further draft amendments to the ODA were introduced, which would have shortened the time of market exclusivity, this time on the basis of profits from sales. The 1992 draft amendment proposed a sales cap of U.S.$ 200 million after which market exclusivity would end for an orphan product, while the 1994 draft amendment suggested that market exclusivity be terminated after four years, unless the sponsor proved that the drug was still of "limited commercial potential". (Rep Waxman, 1994) In this case, exclusivity would be extended for another two years. Neither of the draft amendments were adopted, which was attributed to a lack of willingness on the part of drug developers to disclose their sales data. (Leis García, 2004) Indeed, a hesitant stance towards disclosure of economic data had been said to have brought about the first amendment to the Orphan Drug Act, i.e. the decision to remove the requirement that a company prove the lack of economic viability of a potential orphan drug. By the same token, efforts were unsuccessful to introduce a windfall profit tax on all "profits accruing from the marketing of orphan drugs above a given threshold" (Leis García, 2004, p. 23; refering to Pulsinelli, p. 335-336). This had been implemented in Japan, and it had actually been suggested by the Interagency Task Force of 1979[34]. Even though the above draft amendments were not enacted, they were said to have created a climate of uncertainty which "was significant enough to postpone growth of orphan drug designations and approval for at least five years. […] Such events should remind potential ODA reformers of the sensitivity of rare disease research." (Wellman-Labadie & Zhou,

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[33] For the purpose of the amendment, simultaneous development meant that the second application for orphan drug designation had to be filed no later than six months after the publication of the first designation; clinical trials on which the second application for approval were based upon had to be initiated no more than 12 months after the first applicant's trials, and the application for approval of the second drug had to be submitted no later than 12 months after the application for approval for the first drug. (Rep Waxman, 1990)

[34] The Japanese orphan drug regulation provides for a 1% sales tax on orphan drugs with a profit beyond 100 million Yen p.a. until the subsidy has been repaid. (Wellman-Labadie & Zhou, 2009) Similarly, the Report of the Interagency Task Force on Drugs of Limited Commercial Value underlined that "Sponsors aided through this program who realize a profit must be willing to share such profits, currently or retroactively, to repay in whole or in part, any subsidy or other incentive granted." (Interagency Task Force to the Secretary of Health, 1979, p. 60)

2009, p. 5) Another public health concern which became apparent in the course of the application of the U.S. Orphan Drug Act were so-called pseudo-orphans products. While, under the ODA, only medically plausible subsets of a disease are eligible for orphan designation, the increasing ability to differentiate diseases made it difficult to distinguish between arbitrary and medically plausible subsets. (cf. Leis García, 2004, p. 28 ff.)[35]. Some sponsors 'salami-sliced' common diseases into subsets with low prevalences so that unpatentable products for these subsets, or products whose patenting process moved at a slow pace, became eligible for orphan drug designation. (Thoene, 1991). Critique has also been expressed about the incentive of tax credits, which are said to make the tax payer pay twice for an orphan product – once for the incentive, and a second time if costs for orphan products are reimbursed by health insurance plans. (Seoane-Vazquez et al., 2008)

In sum, the U.S. Orphan Drug Act pioneered legislation to promote R&D for rare diseases, and its financial and non-financial incentives contributed to the development of orphan products. Market exclusivity, tax credits, grants and protocol assistance supported orphan drug R&D at different stages, while pseudo-orphans and blockbuster sales of publically-funded orphan drugs continue to fuel a debate about amendments to the Act, and about incentive-based approaches to promoting orphan drug development in general. Some of the controversial issues surrounding the U.S. ODA were addressed several years later in the process of developing similar legislation in the European Union.

The Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products entered into force on 22 January 2000. (European Parliament and European Council, 2000) Its adoption was preceded by expert and stakeholder consultations, and drew on the experiences made with the U.S. Orphan Drug Act. (European Commission, 1998) The EU Regulation grants ten years of market exclusivity for an authorized orphan product in the European Union, compared to seven years under the U.S. Orphan Drug Act. It stipulates that market exclusivity can be derogated, and another product for the same therapeutic indication can be placed on the market, if the holder of the first authorization

[35] One distinction between an arbitrary and a medically plausible subset would be that the therapy for a medically plausible subset must not be beneficial for the main group of patients. (Enzmann & Lütz, 2008)

consents to it, if he is unable to supply the product in sufficient quantity or if the competing product is clinically superior. Furthermore, a Member State may request to have the status of market exclusivity reviewed after five years based on indicators that the product has become sufficiently profitable. Should sufficient profitability be established, market exclusivity can be reduced to six years. (European Commission, 2008b) The EU Regulation includes fee waivers for services offered by the European Medicines Agency, the volume of which is dependent on whether the applicant qualifies as a small-or-medium-sized enterprise (SME)[36]. Protocol assistance for sponsors of designated orphan products is offered as a form of scientific advice which includes guidance on the significant benefit-criterion[37] for orphan products. (EMEA, 2002; EMEA, 2003) Requests for protocol assistance have steadily increased since the adoption of the Regulation (cf. Table 3-2 below). (EMA, 2006)

Table 3-2 Applications for orphan drug designation and requests for protocol assistance

Year	Designated orphan drugs	Requests for protocol assistance	% of Applications
2000	8	4	50,0%
2001	70	4	5,7%
2002	56	13	23,2%
2003	55	25	45,5%
2004	63	35	55,6%
2005	88	58	65,9%
2006	80	58	72,5%
2007	94	68	72,3%
2008	73	56	76,7%
2009	106	77	72,6%

(Data Source: EMA Annual Reports 2000 – 2009, available at http://www.ema.europa.eu/htms/general/direct/ar.htm, Accessed Jan. 23, 2011)

Since no taxes are levied at European level, the EU orphan drug regulation does not include tax credits. (Dear et al., 2006) Neither does it include research funding; orphan designation, however, makes a sponsor eligible for EU funding earmarked

[36] For non-SMEs, the fee waiver for marketing authorization is 50%, for SMEs it is 100%. (EMA Annual Reports 2000–2009, available at http://www.ema.europa.eu/htms/general/direct/ar.htm, Accessed Jan. 23, 2011)

[37] Art. 3 of EU Regulation No 141/2000 stipulates that a product can receive orphan designation if it can be established, *i.a.* "(b) that 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." (European Parliament and European Council, 2000)

for rare diseases[38]. The EU Regulation calls upon EU Member States to complement EU incentives with mechanisms at national level, such as funding of national research projects, scientific and / or administrative advice or fee reductions, and tax credits[39]. These incentives are collated in an Inventory. (European Commission, 2006b) In the 2006 statutory general report, the European Commission noted, however, that national incentives were still wanting, and that Members States had not satisfactorily complied with the request to report measures which they have established. The European Commission and the EU Council recently renewed their call on Member States to step up national endeavors. (Council of the European Union, 2009; European Commission, 2008a)

To take advantage of the incentives contained in the EU Regulation, a sponsor must prove that a medicinal product is meant to diagnose, prevent or treat a life-threatening or chronically debilitating condition. Furthermore, he must prove that the condition a) does not affect more than 5 in 10,000 people in the Community[40] (prevalence criterion[41]) or b) would not generate sufficient profit to justify the investment (economic criterion). If treatments for the given indication are already available, the sponsor must prove the significant benefit of the product which is subject to the application for orphan drug status (significant benefit criterion). (European Commission, 2000) Significant benefit is assessed twice in the drug development process; once for the designation of a medicinal product as orphan drug, and at this stage with more lenient criteria, and a second time at the point of application for marketing authorization, this time with stricter criteria. (EMA, 2010a) A Committee on Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA) is charged with the Regulation's implementation.

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[38] Funding for rare disease research activities at EU level has been granted through one of the eight Action Programmes of the Framework for Action in the Field of Public Health (1999-2003), in the follow-on First EU Public Health Programme (2003-2008) and currently in the Second EU Public Health Programme (2008-2013) (European Commission, 1998, p. 11). Additionally, funding has been made available under the European Framework Programmes (FP) for Research and Technology Development. (http://ec.europa.eu/research/health/medical-research/rare-diseases/index_en.html)

[39] In fact, in the proposal to the EU regulation, tax credits were considered the most beneficial incentive at national level. (European Commission, 1998)

[40] The prevalence limit for rare diseases in the European Union was initially set in the Community action programme on rare diseases (1999-2003) and maintained in the EU orphan drug regulation.

[41] Experiences from the U.S. Orphan Drug Act had shown that a sole economic criterion did not suffice to encourage the private sector to take advantage of orphan drug incentives, as this criterion required financial disclosures, which, at the point of application for orphan drug designation, may be considered speculative. The prevalence criterion that was added to the U.S. ODA with an Amendment in 1984 was thus included in the EU Regulation from the beginning. (Aymé & Schmidtke, 2007)

Applications for the designation of medicinal products as orphan drugs can be submitted to the COMP at any stage of drug development prior to the application of marketing authorization.[42] Once a product receives orphan drug designation, it is included in the Community Register of Orphan Medicinal Products[43] and becomes eligible for Community incentives. Orphan products are removed from the Community Register a) at the request of the sponsor, b) if, prior to marketing authorization, the criteria for an orphan medicinal product are no longer met or, c) at the end of the period of marketing authorization. During the first four years of the Regulation's implementation, sponsors had the option to apply for marketing authorization either through a centralized or a decentralized procedure. With the adoption of Regulation (EC) No 726/2004, the centralized procedure became mandatory for orphan and for a number of other selected medicinal products. [44] Applications for orphan product marketing approval are thus submitted directly to EMA; once EMA grants marketing authorization, it is binding in all Member States. (European Parliament and Council, 2004) Pricing and reimbursement decisions for orphan products, however, are not taken at the Community level, but by Member States. (Denis et al., 2009) To date, more than 60 drugs with prior designation as orphan products have been approved for marketing in the EU. (OrphaNet, 2010b)

Expenses of activities incurring from the implementation of the EU Regulation are compensated by special budgetary contributions from the European Commission to EMA. (European Parliament and European Council, 2000) In the last decade, the percentage of this contribution of the total EMA budget varied between 0.97 and 5.34%. (Table 3-3)

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[42] Details of the application procedure are available at http://ec.europa.eu/health/files/orphanmp/doc/2007_07/format_content_orphan_applications_rev3_200707_en.pdf.

[43] http://ec.europa.eu/health/documents/community-register/html/orphreg.htm

[44] For products that do not fall under Regulation (EC) 726/2004, marketing authorization can be obtained via a) national authorization procedures for products which are marketed in one Member State only, b) mutual recognition of national marketing authorizations or c) simultaneous applications in several Member States of which one is chosen as reference state; national marketing approval is then granted in the reference and the other applying States (decentralized procedure). (2009)

Table 3-3 EMA budget and orphan drug contributions

Year	EMA total budget[45]	Special contribution (orphan medicinal products fund)	% of total budget
2000	55.287.220	1.000.000	1.81
2001	61.934.000	600.000	0.97
2002	61.304.000	2.750.000	4.49
2003	84.179.000	3.100.000	3.68
2004	99.089.103	3.985.000	4.02
2005	111.835.000	5.000.000	4.47
2006	138.676.000	7.400.000	5.34
2007	165.298.000	4.892.000	2.96
2008	182.392.000	3.755.000	2.06
2009	196.135.000	5.632.000	2.87

(Data Source: EMA Annual Reports 2000 – 2009, available at http://www.ema.europa.eu/htms/general/direct/ar.htm, Accessed Jan. 23, 2011)

The majority of the expenses are shared between fee waivers for protocol assistance and for applications for marketing authorization; smaller amounts are used for inspections and for post-authorization fees. (EMA Annual Reports 2000–2009, available at http://www.ema.europa.eu/htms/general/direct/ar.htm, Accessed Jan. 23, 2011)

In the year 2005, five years after the Regulation's implementation, the European Commission concluded that the response to the European orphan drug regulation had by far exceeded earlier expectations. The time which had elapsed since the enforcement of the Regulation, however, was considered too short to assess its ultimate public health benefits.[46] Instead, the Regulation's benefits were assessed by a set of alternate parameters, i.e. a) the benefit to patients (number of patients which potentially benefit from the legislation / the interaction with patient organizations), b) the impact on clinical trials and compassionate use programs (status of orphan drug development / impact of protocol assistance on clinical trial quality) and c) the stimulus for orphan disease research (level of innovation of orphan products / level of awareness of orphan diseases / establishment of networks of experts). (EMA,

[45] EMA's budget is comprised of fees paid by the pharmaceutical industry, of EU budget contributions and miscellaneous other income. In 2009, 75,1% of the budget came from the pharmaceutical industry, 23.9% from the EU and 1% from other sources.

[46] These, according to the Report, would have to be the "increase in the survival, the life expectancy and / or the quality of life of patients affected by rare disorders" ((European Commission, 2006a, p. 8)

2005, p. 17 ff.) 53% of the products for which applications for orphan drug status were submitted were novel or innovative products, 40% of the marketed orphan products between 2000 and 2005 were for conditions for which no treatment had been available before, while for the remaining 60%, a significant benefit to patients regarding efficacy, safety or contribution to patient care was expected. Special mention was made of the exchange with patient organizations and the benefit of dialog (the COMP is the first decision-making committee in the EU that includes patient representatives as full members). The EU Regulation had also raised the awareness for rare diseases, as a Medline publication count carried out by COMP had revealed. Furthermore, knowledge exchange and networking was fostered; more than 350 experts had been documented in the COMP database in the first five years of the Regulation's implementation, who ensure competent reviews of orphan drug applications and reflect a growing interest of scientists in rare diseases. The Report did not call for amendments to the Regulation, yet it was acknowledged that a number of issues were in need of clarification. Among these are the duration of market exclusivity for a second product for the same orphan indication[47] and the definition of sufficient profitability, or an acceptable return on investment to initiate the procedure for a possible derogation of market exclusivity. (European Commission, 2006a)

It has been argued that, to stay "in line with spirit of legislation", a review of market exclusivity should take into account all indications for which an orphan product is used. (Denis et al., 2009, p. 91) At present, designated orphan products can only be approved for marketing for the applied orphan indication. However, once an orphan product is on the market, the same product can receive marketing approval for other indications. Prevalences are not added up following such extension, so that an orphan product may keep its status even if it exceeds the prevalence limit for which it originally received market exclusivity. Also, a drug for a more common indication which proves effective for a rare disease can be approved as an orphan

[47] The Regulation states that a second product which shall be authorized for an orphan indication, will share market exclusivity with the first approved product for the remainder of the first product's exclusivity period; it had not been determined though, whether the second product will receive its own ten year exclusivity.

drug with a different name (and a new price) for this rare indication.[48] The EU Commission acknowledged that differences in pricing and reimbursement policies between the Member States caused problems with access to orphan drugs. A survey on the availability of 12 orphan products which had received market authorization before December 2003, revealed that one year after their approval, there was only one Member State in which all 12 products were available. In only 12 of the then 25 EU Member States, 6 of the 12 products were available. The time which had elapsed between authorization and availability ranged from 35 to 212 days. In numerous cases, the products were not available at all; incomplete hospital records made it difficult, however, to exactly determine drug availability. Still, the issue was considered very serious, as patients with rare diseases should not be made to wait excessively for authorized products to become available to them. (EMA, 2005; EMA, 2006) In the absence of a European regulation, pricing and reimbursement is negotiated by Member States, and the outcome of such negotiations in the first Member State often serves as a reference for subsequent negotiations in other states. This procedure has been criticized as an incentive for the private sector to begin negotiations in states which are known for their generous pricing and reimbursement policy. Rising costs for orphan products are made partly responsible for "[…] an additional upward pressure on health care budgets and may challenge the limits of solidarity between citizens." Consequently, "[…] high prices combined with the growing budget impact of orphan drugs also negatively affect the image of the orphan drugs among decision-makers." (Denis et al., 2009, p. iv) Setting prices at the European level, so the authors argue, instead of the level of Member States, could ensure that the expected (and hoped-for) increase in the number of orphan products will not overstrain health insurance budgets and put "the success [of the orphan drug legislation] at risk." (Ibid., p. 92)

Five years after the Regulation's implementation, EBE and EuropaBio, an association of over 75 bioindustries worldwide, published a White Paper on the European regulation. The organization gave strong support to the regulation, but put forward nine suggestions to "optimize the framework around it." (for this and the

[48] Denis et al. identified three twin products (Savene®/Cardioxane®, Siklos®/Hydrea® and Revatio®/Viagra®) of which one has an orphan indication, and the other does not. In all three cases, the orphan product was sold at a higher price. (p. 89)

following cf. EBE / The European Association for Bioindustries (EuropaBio), 2005) The suggestions partly concurred with deficits already identified in the reports by the COMP and the European Commission, *i.a.* the lack of a definition for the notion of sufficient profitability. In addition, the Association called upon the European Commission to provide clear guidance on the significant benefit criterion, requesting that the present practice be kept, i.e. that the clause is not applied very strictly at the beginning of the application process for orphan designation. For many companies, so EBE and EuropaBio argued, a strict application of the requirement to prove significant benefit would mean that the sponsor has to have clinical data available before it applies for orphan drug designation. These data are rarely available for rare diseases, so that a stricter ruling on the significant benefit criterion could hamper research efforts. With regard to compassionate use-programs, i.e. making drugs available to patients before regulatory approval, EBE / EuropaBio suggested that all EU Member States follow the example of France, Italy and Belgium and pay for the supply of compassionate use-drugs. Many orphan medicinal products are, according to the Association, developed by small and medium-sized enterprises which cannot financially support long-term compassionate use-programs. (EBE / The European Association for Bioindustries (EuropaBio) 2005)

To summarize, the incentives contained in the EU regulation on orphan drugs gave momentum to the development of orphan products in the European Union. At the same time, key public health issues, such as timely access to orphan drugs for patients in all EU Member States, harmonized reimbursement policies and affordable pricing, formulating an understanding on the significant benefit criterion and on the notion of sufficient profitability, still need to be addressed. The authors of the 2009 study on Policies for Orphan Diseases and Orphan Drugs issued the warning that: “The spirit of the legislation, being to stimulate research and development on drugs for diseases that would otherwise be neglected by industry and academia, is put at risk by this situation, as high prices also mean high budget

impacts and in general low cost-effectiveness in comparison to non-orphan drugs." (Denis et al., 2009, p. 90)[49]

3.1.1 Orphan Drug Regulations: R&D Incentives for Neglected Diseases?

Both rare and tropical (neglected) diseases had been part of the initial concept to develop incentives for drugs of limited commercial value, which laid the foundation for the U.S. Orphan Drug Act. When the U.S. ODA was formulated eventually, however, reference to tropical diseases was made rather "incidentally" (Milne et al., 2001, p. 10). The conclusion of a House Committee hearing in 1982 explained that "The term 'rare in the United States' is used to assure that the benefits of this bill apply to drugs for diseases or conditions which are rare here, even if prevalent in other countries. To the extent that this provision encourages the development of drugs for prevalent diseases in developing countries, the committee believes it is sound public policy." (Orphan Drug Act: Report from the Committee on Energy and Commerce, United States House of Representatives. Report 97-840, Part I. in Milne et al., 2001, p. 10) In the spirit of this argument, Haffner (1991) underlined nearly a decade later that „The orphan products program is concerned with and directed at public health needs and problems beyond the borders of the United States. While a given disease or condition may be rampant in some developing nation or area of the world, if its prevalence fits the orphan definition, or if it is clear that sales of the product 'in the United States' would be insufficient to stimulate is [sic] development and distribution, then the orphan drug provisions are available to its sponsor. One of the objectives of the program is to stimulate the medical and pharmaceutical community in the United States to develop products to meet the needs of populations elsewhere." (p. 611-612) Interestingly though, the applicability of the U.S. ODA to neglected diseases, which had been named an implicit public health objective of the legislation, later appeared to surprise. „One unexpected consequence of orphan legislation", so Haffner et al. noted, "has been the realization that many infectious diseases that are highly prevalent in developing areas of the world qualify for incentives to develop orphan drugs in developed

[49] For further discussion on the issue surrounding cost-effectiveness of orphan products see (Clarke, 2006; Dear et al., 2006; Marshall, 2005; Owen et al., 2008; Wellman-Labadie & Zhou, 2009; Drummond et al., 2007; Thamer et al., 1998; CPTech, 2005b)

countries, such as in the USA.“ The authors conclude that “this decision is an aspect of orphan-drug legislation that might benefit from more vocal dissemination. (Haffner et al., 2008, p. 2043) Indeed, in 2009, the U.S. National Institutes of Health (NIH) launched a new program for rare and neglected diseases, based at the NIH Office of Rare Diseases Research, and endowed with $24 million for the fiscal year 2009. The Therapeutics for Rare and Neglected Diseases Program (TRND) focuses on preclinical research, taking account of the fact that in the private sector, often promising compounds for both groups of diseases are not followed through to preclinical or clinical stages of research and development. The TRND aims to increase the number of Investigational New Drug (IND) applications for both groups of diseases, which could then be handed over to experienced companies to perform clinical trials. (NIH, 2009)

Following the implementation of the European orphan drug regulation, European legislators were convinced that these could serve as a model for stimulating research into neglected diseases. At a Round Table on Access to Medicines in 2003, the then President of the EU Commission, Romano Prodi, declared that […] “the Commission will consider the need for a specific legislative instrument to incentivise R&D for neglected and poverty diseases, along the lines of the EU Orphan Drug Regulation”. (Prodi, 2003) Several months earlier, Erkki Liikanen, Member of the European Commission, took the occasion of a Round Table on the lack of R&D for neglected diseases to underline the potential of the EU orphan regulation, stating that „[t]his kind of mechanism works. [...] We believe that this legislation could support the development of medicines for certain neglected diseases!” (Liikanen, 2002) A study of the Fraunhofer Institute, conducted in 2003 on the Impact of Regulation on the Development of New Products in the Pharmaceutical Sector, seconded this opinion, stating that the EU Orphan Drug Regulation might serve as a source for concepts to foster research and development for neglected diseases. (Bührlen B et al. 2003) The EU orphan drug regulation stipulates, however, that products have to have a significant benefit for citizens in the European Union; therefore, “diseases in developing countries will not be able to benefit from the EU orphan status”. (European Commission 2006; p. 5) EMAs Committee for Orphan Medicinal Products had addressed the issue in its Report in 2005, postulating that: “To support the development of medicinal products for neglected diseases in less developed regions of the world, the COMP would like to

be in a position to designate medicinal products for the so-called neglected diseases in the future. This could be achieved by waiving the significant benefit criterion in such cases and would be consistent with Commission policy in the Framework Programmes for research and technology development." (EMA, 2005, p. 3) In its most recent Road Map to 2015, which named 'addressing public health needs, particularly unmet medical needs for rare and neglected diseases' a strategic area, EMA renewed its interest in contributing to R&D for neglected diseases. (EMA, 2010b)

Opinions on the desirability and the feasibility of applying orphan drug incentives to neglected diseases differ considerably. While Dear et al. (2006) consider it appropriate for neglected diseases to benefit from orphan drug status, given the difference in resources between Europe or the U.S. and endemic countries of neglected diseases, Villa et al. (2009) have doubts regarding the political feasibility and the public support that needs to be generated for such proposals, especially in times of cuts in health spending. Market exclusivity, on which the success of orphan drug regulations seems to hinge, is considered irrelevant in the resource-poor settings of neglected diseases, that is in environments without functioning and financially well-equipped health coverage programs (WHO, 2006e; Trouiller et al., 1999) To illustrate, in Africa and in Latin America, only 8% and 35% of the population, respectively, have two-thirds of their drug costs reimbursed, compared to 80-100% of the population in Europe. (Trouiller et al., 2002, p. 2191) Tax credits, an orphan-drug incentive, do not offer a profit in the R&D process. It has been argued, however, that they may at least reduce investment losses for neglected diseases. (Anderson, 2009) The WHO-CIPIH Final Report observed that "[…] there is evidence that general tax credits have an impact on market-driven R&D.", yet it qualified that, in the absence of markets and profits, "even a 100% tax relief would have no stimulating effect." (WHO, 2006e, p. 87) Several proposals have been put forward to complement or amend orphan drug regulations to fit the particular needs of neglected diseases. Transferable market exclusivity could grant a sponsor of a drug for a neglected disease market exclusivity for a drug of his choice to compensate him for the low return on investment. Alternatively, transferable market exclusivity could be granted to a sponsor "for all products with the same active moiety" as the drug for the neglected disease (Milne et al., 2001, p. 50). Also, defining all neglected diseases as orphan diseases according to the economic

criterion would make them eligible for all incentives under orphan drug regulations. (Villa et al., 2009) The WHO Expert Working Group on 'Research and Development. Coordination and Financing', which received and evaluated proposals for innovative financing for neglected diseases, included orphan drug schemes in its list of potential mechanisms, yet it acknowledged shortcomings for neglected diseases in the current legislation that would have to be dealt with. Thus, apart from the absence of a viable market, the Working Group pointed to the lack of requirement for regulators to ensure that products are suitable for use in endemic developing countries. (WHO, 2010e)

Under the U.S. Orphan Drug Act, neglected diseases are eligible for orphan drug incentives, if "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered [sic] from sales in the United States of such drug". (United States Congress, 1983) Malaria and human African trypanosomiasis have, in fact, been defined as "rare" under the U.S. Orphan Drug Act's epidemiological criterion "…based on the few cases recorded on the American territory and linked to individuals returning from endemic areas." (Villa et al., 2009, p. 35) In general, however, it has been found that little use has been made of orphan drug regulations for neglected diseases. (WHO, 2010e) Villa et al. (2009) noted that "[a]chievements for neglected tropical diseases have been minimal under orphan drug laws compared to what has occurred for rare diseases." (p.35) By the year 2002, only 12 of the 238 market approvals under the U.S. Orphan Drug Act had been for tropical diseases, most of them travel diseases. One reason may be that orphan drug regulations do not offer incentives or funds for preclinical research. (Anderson, 2009)

The debate in the public health community about the application of orphan drug incentives to neglected diseases is ongoing (cf. Baker, 2004; Milne et al., 2001; Trouiller et al., 1999; Villa et al., 2009), and orphan drug regulations have been named one option whose reforms to include incentives for neglected disease R&D "are awaiting legal answers". (Leis García, 2004, p. 1)

3.2 Option 2: The draft Medical Research and Development Treaty (MRDT)

Another approach to a regulatory solution for the R&D deficit for neglected diseases was taken with the draft Medical Research and Development Treaty (MRDT) (CPTech, 2005b). The concept for this Treaty was introduced in 2002 (Love & Hubbard, 2007) and submitted for evaluation to the WHO Commission on Intellectual Property, Innovation and Public Health (CIPIH) in February 2005. The MRDT does not exclusively address R&D for neglected diseases, as orphan drug regulations target rare diseases. Instead, its authors and sponsors[50] proceeded from the view that the current system of funding for medical R&D, based on patents and high drug prices to recoup investment, is ineffective and expensive. (Love & Hubbard, 2007) It is argued that it further impedes equitable access to innovative treatments and, from a public health point of view, misdirects investments from public health priorities towards drug marketing or highly profitable, but less urgent areas of medical R&D. To illustrate, the authors underline that, of the new drugs approved by the U.S. Federal Food and Drug Administration (FDA) between 1990 and 2004, only 22.5% had a significant benefit over previously approved products, and less than 1% of the drugs approved between 1989 and 2000 were developed for diseases of poverty. Additionally, only 10% of drug sales went into research and development activities, and of these 10%, only 20% were invested in innovative products. (Hubbard & Love, 2004; Love & Hubbard, 2007) To correct these imbalances, the MRDT proposes that signatories commit themselves to national funding obligations for medical research and development. The governing bodies to be established with the Treaty would not collect and distribute funds, but set funding levels and monitor funding flows. The level of obligatory national funding would be based on shares of GDP, or per capita income.[51] Several options are provided for signatory states to meet their financial obligations; these include direct public funding of medical research projects, offering tax credits, contributing to philanthropic spending or to prize funds for medical innovation. A Council for

[50] The MRDT was submitted to the Commission for evaluation with an open letter signed by 162 scientists, public health experts, lawyers, economists, government representatives and parliamentarians. (CPTech, 2005a)

[51] Thus, high income countries would spent 15 basis points of GDP on medical research and development and 2 basis points on priority research, of which at least half would be allocated for neglected diseases. (CPTech 2005b)

Medical Innovation[52] (CMI) would "review minimum levels" of financial contributions every two years (CPTech, 2005b, p. 6) and monitor their achievement. (CPTech, 2005b, p. 8) The CMI would also be tasked with drawing up regulations to measure and report financial flows, and assemble and publish funding mechanisms in signatory states in biennial reports. (CPTech, 2005b, p. 8) A Committee on Priority Medical Research and Development (CPMRD) would be appointed to set "global targets for priority medical research and development (PMRD)" every two years in the areas of vaccine development, neglected diseases, global infectious diseases, databases, research tools and other public goods, health systems and appropriate technology, preservation and dissemination of traditional medical knowledge and "other appropriate priority research"; these targets would be evaluated annually (CPTech, 2005b, p. 6) Further specialized committees on open public goods, technology transfer or on exceptionally productive and useful projects would be established to identify qualifying projects. As an incentive to invest into these projects, investments would be counted towards the financial obligations of a State under this Treaty; investments in priority research that exceed a State's obligations could, similar to the Kyoto Protocol-procedure, be transformed into tradable credits or certificates. No more than one third of a State's obligations, however, shall be served by special credits. (CPTech, 2005b, p. 9) To improve access to innovation, promote knowledge-sharing and discourage me-too-products, the authors and sponsors of the Treaty suggest to separate innovation incentives from drug prices through the creation of prize funds. Prizes would be tied to the obligation of allowing generic production of the rewarded product; the level of the reward would reflect the health impact of the innovation, thus aiming to discourage investment in me-too products. (Love & Hubbard, 2007)[53] The Treaty further stipulates that the signatories will "adopt procedures concerning obligations for research supported by the public sector to be made available to the public through open access archives or repositories." (CPTech, 2005b, p. 10)

The Committee on Medical Innovation (CMI) would be charged with adopting "regulations that ensure equitable access to government funded inventions."

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[52] The Treaty would be governed by an Assembly for Medical Research and Development, a Council for Medical Innovation, six Committees, and have a Permanent Secretariat.

[53] For the ongoing debate on prize funds see e.g. http://keionline.org/prizes

(CPTech, 2005b, p. 10) For a limited time period, patents shall not be submitted for data which stem from qualifying open public goods.

In addition to funding for medical R&D, the Treaty addresses a broad range of issues relating to medical research and development, which the signatories of the Treaty would be encouraged to promote. (CPTech, 2005b) Table 3-4 below gives an overview of objectives pursued and mechanisms proposed in the MRDT.

Table 3-4 The Medical Research and Development Treaty: Aims and Mechanisms

Objectives	**Eligible finance mechanisms include**	**Eligible for tradable credits (max. one third of all funding obligations)**
Adequate and predictable sources of finance	Direct public funding of profit or non-profit research projects	investment in priority medical research (*i.a.* in R&D for neglected diseases)
Cost-effective incentives	Purchases of relevant medical products (if this creates R&D incentives)	investment in open public goods
Equitable access	Preservation and dissemination of traditional medical knowledge	investment in technology transfer
Facilitation of follow-on research	Payment of royalties to patent owners	investment in exceptionally productive and useful projects
Fair allocation of cost for medical R&D	Tax expenditures	
Knowledge sharing	Innovation prizes / incentives	
Needs-based priority setting	Philanthropic expenditures	
Support of diversity and competition	Government-obliged expenditures by businesses or non-profit organizations / research funding obligations on sellers of medicines	
Transfer of technological knowledge and capacity		

Data Source: Medical Research and Development Treaty (MRDT), Discussion draft 4. http://www.cptech.org/workingdrafts/rndtreaty4.pdf

Debates in the scientific community accompanied the introduction of the concept of a medical R&D Treaty, and the arguments brought forward suggest a separation of responses into three groups. While a first group gathers supporters of the proposed Treaty and its mechanisms, a second group doubts the Treaty's political and technical feasibility. The third group assembles respondents who either reject the Treaty concept on the grounds of anticipated undesirable impacts on pharmaceutical research and development, or on the argument that the Treaty concept is based on wrong premises.

Favorable analyses of the concept highlight the necessity of a shift in paradigm (Dentico & Ford, 2005) and of the steering function of a prize fund, which would disincentivize the development of me-too-products, and direct research priorities towards public health needs. Additionally, access barriers would be removed as drug producers, after having received their innovation reward, would pool patents for generic production. (Winters, 2006; Faunce & Nasu, 2008) Among more skeptical reviewers, the Treaty is credited with playing a valuable role in drawing attention to these issues (Orsenigo, 2005), yet the question is raised whether the mechanisms proposed in the MRDT could easily coexist alongside the current patent system, or whether a smooth transition from one system to the other could be managed. (Orsenigo, 2005; Farlow, 2007) Furthermore, difficulties are anticipated in distinguishing medical from other intellectual property, whereby the latter would not be covered by the MRDT. (Farlow, 2007) The flexibility of mechanisms that the Treaty offers to fund medical R&D is considered "commendable" (Tren & Bate, 2006, p. 3)[54], yet critics point to a lack of enforcement mechanisms for these funding obligations. (DiMasi & Grabowski, 2004) Furthermore, it is argued that numerous measurements and sophisticated accounting systems would have to be installed, also in developing countries, to track financial flows. Also, shortfalls are named in the system of tradable credits[55], and the option of fulfilling Treaty obligations with the purchase of high-priced drugs is seen as undermining efforts for cost-efficiency and encouraging waste. (Farlow, 2007)

In addition to those critical of what may be summarized as issues of the feasibility of the Treaty's provisions and mechanisms, there is a stark opposition to the perspective that under the MRDT, research priorities would be set by public institutions, and not by the private sector. Firstly, so it is argued by the Treaty's opponents, research organizations have adequate research agendas and select innovation priorities according to consumer needs and preferences. If these preferences are not be shared by "government research czars" (DiMasi &

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[54] Apart from acknowledging the funding flexibilities provided for by the Treaty, Tren and Bate (2006) consider the document to be „unworkable", „impractical" and based on wrong premises.

[55] Farlow (2007), for instance, argues that a common denominator would be needed for trading credits, that it is unclear how and whether risk-bearing, basic research, generic products or cheap, yet effective measures of prevention would be measured and counted, and that high income countries would have little incentive to provide low-income countries with inexpensive medicines as long as buying drugs for high prices fulfills the high-income-country's Treaty obligations.

Grabowski, 2004, p. 10), relevant projects may not receive funding under the direct funding scheme of the MRDT. Additionally, it is feared that governments will find it difficult to correctly value innovations, and thus be tempted to offer research prizes that are too small, but which a company that has already spent its investment will have no other choice than to accept. (DiMasi & Grabowski, 2004; DiMasi & Grabowski, 2007) The MRDT is also considered to be vulnerable to corruption and rent-seeking from various sources and with varying effects. Staff in the public sector, so it is argued, may lack adequate knowledge compared to research organization's staff; therefore, it may be susceptible to political lobbying and be guided by the wrong motives when selecting research priorities. "Asymmetric information" would then lead to "adverse selection" to the point where "the best organized und funded [patient] groups succeed the most in influencing allocative choices", and "[…] innovator firms [are turned] into contract research organizations […]". (DiMasi & Grabowski, 2004, p. 7) On the other hand, if those public institutions that determine innovation prizes have extensive discretionary powers, they may also be subject to lobbying efforts by research organizations, and pay prizes that exceed the investment. (Faunce & Nasu, 2008) Lastly, doubts are being cast on the validity of the premises on which the call for a paradigm shift and the Treaty concept are based, i.e. the R&D deficit and the public health relevance of neglected diseases. Treatment deficits, so it is argued, are access deficits caused by inadequate health infrastructure, taxes levied on drug imports, or ill-directed spending by endemic countries, e.g. into defense instead of health or education budgets. Low mortality rates for neglected diseases and the increasing burden of non-communicable diseases, also in developing countries, justify current R&D priorities since these will benefit patients in the developed and the developing world. (Stevens, 2004)

In 2005, the European Parliament produced a report on major and neglected diseases in developing countries which supported the concept of a medical R&D treaty and "[u]rges, in the context of the WHO Commission on Intellectual Property, Innovation and [sic] Health, a new global medical R&D treaty, including minimum obligations to support R&D, priority setting mechanisms and consideration of a system of tradeable [sic] credits for investments in particular projects;". (European Parliament, 2005, p. 11) The WHO-CIPIH, in its Final Report, acknowledged that the Treaty "[…] seeks to address the fundamental policy

dilemmas in promoting innovation and access relevant to public health, and has initiated a useful debate.", yet it observed that "[m]any comments emphasized that the proposal was set out in a broad-brush fashion, making it difficult to assess, without further information and analysis, how various legal, financial, technical and institutional issues could be addressed, as well as genuine concerns about political and practical feasibility." (WHO, 2006e, p. 90) While "[r]ecognizing the need for an international mechanism to increase global coordination and funding of medical R&D", it recommended that "the sponsors of the medical R&D treaty proposal should undertake further work to develop these ideas so that governments and policy-makers may make an informed decision." (Ibid., p. 91) Consequently, the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, adopted by the World Health Assembly in May 2008, listed among the "actions to be taken to promote research and development […]" to "encourage further exploratory discussions on the utility of possible instruments or mechanisms for essential health and biomedical R&D, including inter alia, an essential health and biomedical R&D treaty". (WHO, 2008, p. 11&27) However, the WHO Expert Working Group on Research and Development Financing, established on the basis of the Global Strategy and tasked to „examine current financing and coordination of research and development and proposals for new and innovative sources of financing, to stimulate research and development related to types II and III diseases and the research and development needs of developing countries in relation to Type I diseases." concluded in its 2010 Report that a "biomedical research and development treaty" did not meet the criteria which the Expert Working Group had established for the selection of proposals to be evaluated as new and innovative sources of financing.[56] (WHO, 2010e, p. 86) The proceedings and conclusions of the Expert Working Group were sharply criticized (López Montaño, 2010; HAI, 2010) In response to a "divergence between the expectations of the Member States[…] and the output of the [EWG]…", (WHA, 2010, p. 1), a follow-on Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) was set up to take forward and deepen the work of the EWG, under careful observance of scientific integrity and

[56] All proposals submitted to the EWG were screened and short-listed on the basis of impact on health in developing countries, operational efficiency and feasibility and financial aspects. For a detailed description of the screening and evaluation methodology, s. http://www.who.int/phi/documents/RDFinancingEN.pdf, p. 81 ff.

the absence of any conflict of interest. (Ibid, p. 3)[57] The CEWG reconsidered the six proposals which the EWG had excluded as proper mechanisms, which included the draft Medical Research and Development Treaty, as well as the proposal for a global framework. In its Final Report of April 2012, the WHO-CEWG judged the proposals for the treaty and the global framework to be "ambitious", yet concluded that the concepts were promising and comprehensive enough to recommend the launching of negotiations. Consequently, the Working Group proposed that Member States enter into formal negotiations during which "[…] key steps necessary to begin implementation and the financial feasibility of the proposals […] should be deliberated […]." (WHO, 2012g, p. 53) The WHO-CEWG is due to present its Final Report to the 65th World Health Assembly in May 2012.

3.2.1 The MRDT: A Solution for the Deficit in Neglected Disease R&D?

The Medical Research and Development Treaty is based on the premise that medical R&D does not take sufficient account of public health needs and instead responds to market values of interventions, clearly illustrated by the lack of R&D for neglected diseases. It aims to ensure adequate and predictable flows of financing, cost-effective incentives, a fair distribution of the burden of cost, as well as knowledge-sharing, capacity-building, technology transfer, follow-on research and priority setting for the benefit of public health needs. The Treaty seeks to establish a system of national financing obligations for medical research and development, based on a wide array of R&D funding mechanisms that the signatories may chose from to meet their obligations. While it is agreed, even among critics of the concept, that an exclusive reliance on patents to encourage medical innovation contributes to access and R&D deficits in the area of neglected diseases, reservations are expressed whether the MRDT offers the right solutions. The MRDT is criticized as being politically unfeasible (Farlow, 2007; Orsenigo, 2005), lacking clear enforcement mechanisms and as being an instrument which may promote national protectionism. (DiMasi & Grabowski, 2004) The current patent system to protect medical innovation, so it is argued, may well be supplemented with prizes or other incentives as in orphan drug regulations, but it

[57] For the issue of conflict of interest in both WHO working groups, cf. a. http://www.keionline.org/node/1058

must not be weakened or supplanted. And while some analysts suggest that debates shall continue about the public benefit of this and other schemes of reform, (Faunce & Nasu, 2008) others argue that even to pursue the debate of this instrument was a waste of time and resources which could better be devoted to strengthening existing and productive product development partnerships. (Farlow, 2007) Some analysts of the MRDT suggest alternatives, such as a partial socialization of costs for clinical trials (Orsenigo, 2005), or an extension of orphan drug regulations to neglected diseases (Tren & Bate, 2006). Advocates conclude, however, that it would be short-sighted to continue to rely on philanthropic spending or public funding efforts if these were not embedded in a strategy of sustainable financing to meet current and future health care challenges. (Winters, 2006)

4 Methods

4.1 Operationalizing the Research Question

Orphan drug regulations and the draft Medical Research and Development Treaty have long been discussed in the scientific community as regulatory approaches to promote R&D into neglected diseases. The aim of this research project was to gather quantifiable data among stakeholders with which to accompany these ongoing reflections, debates and the path to political decision-making. Two key differences between orphan drug regulations and the MRDT had to be taken into account in the operationalization of the research question: Firstly, orphan drug regulations were developed to promote drug development for rare diseases, while the MRDT takes a broader approach and "[…] recognizes the importance of ensuring sustainable sources of finance for innovation, including R&D for neglected diseases and other public health priorities, […]". (CPTech, 2005a, p. 3) Secondly, at the time of this writing, orphan drug regulations have been in force for nearly three decades, while the MRDT is in draft status. In view of these differences, we did not formulate the research questions to compare and contrast the performance of both instruments. Instead, the concept of the project was to decouple incentives and measures from their instruments, and to gather data on the following key questions:

- **Which are the most important causes for the deficit in R&D and treatments for neglected diseases?**
- **Which measures are desirable and feasible to promote R&D into neglected diseases?**
- **Is it desirable and feasible to develop a regulatory instrument to promote R&D into neglected diseases?**

The question on the causes for the treatment deficit for neglected diseases was included into the survey to identify such causes which a regulatory instrument to promote R&D would have to respond to. For the purpose of the question on measures to promote R&D into neglected diseases, key measures of orphan drug regulations, of the MRDT, as well as proposals gathered from literature search were

submitted to the participant's assessment. Furthermore, the participants in the survey were asked to contribute proper suggestions for measures to promote R&D into neglected diseases.

The questionnaire for the first round included a section on orphan drug regulations for rare diseases, since we were interested to learn how familiar the survey participants are with orphan drug regulations, and how they judged the regulations' performance for rare diseases. The section on the performance of orphan drug acts for rare diseases was not carried forward into the second round of the survey.

Against the background that no precise definition exists for neglected diseases, and that such definition may be required in a regulatory instrument, the survey participants were asked to name criteria to define neglected diseases, and to rank these according to importance.

We were aware that the approach which we selected precluded an answer to the question of the desirability and feasibility of either instrument for neglected diseases. It would, however, allow us to learn from the stakeholders which measures they recommend to promote R&D for neglected diseases, irrespective of the measures' current association with a regulatory concept. Our approach was based on the assumption that a regulatory instrument to promote R&D into neglected diseases may also rely on selected or modified incentives contained in orphan drug regulations, or include a selection, but not all of the measures proposed by the MRDT.

4.2 Description of Methods

Several methods lend themselves to the realization of such research question, among them focus groups, face-to face meetings, face-to-face interviews, telephone interviews or opinion surveys. (cf. Geyer & Siegrist, 2003; Behnke et al., 2006) We selected the Delphi method, since it allowed us, firstly, to conduct the survey online so that we were able to invite potential survey participants globally, i.e. from developed, developing and threshold countries. Secondly, it enabled us to contact, and possibly include, a large number of survey participants. Thirdly, a Delphi survey provides for the collection of both full-text and quantitative data. Lastly, the method goes beyond an opinion survey, and offers an anonymous forum for the

exchange of ideas and opinions among the survey participants. To analyze full-text responses gathered in the course of the survey, we selected the text-sorting technique by Beywl and Schepp-Winter (2000). The following sections describe the methods used and the application to our research project.

4.2.1 The Delphi Method

In a Delphi exercise, experts, or stakeholders, for a specific subject are asked to respond to several rounds of a survey. Characteristic for the Delphi method is the anonymity of the panel and the fact that feedbacks containing results of previous rounds are forwarded to the panel with each new round of survey. (Sackman, 1975) Some Delphi surveys allow participants to give brief explanations around their replies, which are also made available to the panel, together with the statistical analyses of the quantitative items. Against the background of this information, the panel members are asked to reconsider their estimates of the previous round. (de Meyrick, 2003) Delphi surveys thus differ from opinion surveys in that the participants "answer from the second round on under the influence of their colleagues' opinions". (European Commission, 2006c) The procedure aims to stimulate cognitive processes as in group discussions while anonymity shall eliminate negative group processes such as opinion leadership, peer-pressure, the influence of individual powerful personalities or the effects of status. (Häder, 2002) Delphi surveys are said to allow the respondents to state their opinion free from the constraint of group processes, and to receive the opinions of co-respondents equally free from distorting public images. (de Meyrick, 2003)[58]

The development of the Delphi technique dates back to 1948 at the Rand Corporation. (Sackman, 1975) The "definitive paper" (de Meyrick, 2003, p. 9) on the method was only published in 1963, as initial Delphi studies had dealt with unpublished defense research issues. In the years to follow, Delphi surveys were increasingly used outside the area of defense research, particularly as forecasting devices and in technology assessment, thereby "respond[ing] to a demand for improved communications among larger and/or geographically dispersed groups which cannot be satisfied by other available techniques." (Linstone & Turoff, 2002,

[58] For an analysis of group processes cf. a. (Dalkey, 1969)

p. 11) Originally, the goal of the technique was "to obtain the most reliable consensus of opinion of a group of experts […] by a series of intensive questionnaires interspersed with controlled opinion feedback. " (Ibid, p. 10) Today, Delphi surveys are applied in various disciplines to research questions for which "accurate information is unavailable or expensive to obtain, or evaluation models require subjective inputs to the point where they become the dominating parameters." (Linstone & Turoff, 2002, p. 10) Building on the concept of what has been labeled the "conventional Delphi" (Sackman, 1975, p. 8 ff.), different forms of Delphi surveys have evolved under the labels quantitative Delphi, reactive Delphi, modified Delphi, normative Delphi or exploratory Delphi. Some labels refer to "the type of application, some to the method of 'scoring' used and some just imply that the approach is different […]". (Mullen, 2003, p. 38) Between the early 1950s and 1994, over 1.000 projects applied or discussed the Delphi method; the most popular areas of research that used the Delphi technique were business, education and health care. (de Meyrick, 2003) Delphi applications in health care and medical research questions are known since the 1960s. (Ammon, 2005; Day J & Bobeva M, 2005; Linstone & Turoff, 2002; Mullen, 2003; Scholles, 2006) For the time period of 1995 to 2001, de Meyrick (2003) identified 33 Delphi studies related to medical issues, of which three dealt with health policy questions. Recent Delphi surveys on global health issues explored priority setting to combat non-communicable diseases (Daar et al., 2007), or examined public health-sensitive patent legislation. (Costa Chaves & Oliveira, 2007)

Delphi surveys allow for rankings and priority-setting which is considered operational also for policy-makers. (European Commission, 2006c) Assessments of the required expenditure for Delphi exercises vary. While O'Loughlin & Kelly (2004) referred to low administrative costs for a Delphi survey, the European Commission considers it a disadvantage of Delphi surveys that they are "fairly time-consuming and labour intensive and require (external) expert preparation. They are therefore expensive." (European Commission, 2006c) For the experts who participate in a Delphi exercise, "[…], it provides a communication device […] that uses the conductor of the exercise as a filter in order to preserve anonymity of

responses." (Helmer, 1977, p. 19)[59] Critics have argued that the anonymity in Delphi surveys may deliver the respondents from the responsibility of his or her views, and lead to a "circular buck-passing". (Sackman, 1975, p. 52) Especially in Delphi exercises that strive to reach a consensus, anonymity is said to run the risk of veiling respondents who are less committed to the issue, and who adopt the majority opinion to expedite the exercise, thus promoting an artificial consensus. (de Meyrick, 2003)

Linstone & Turoff (2002, p. 4) recommend to consider a Delphi survey if a problem "cart benefit from subjective judgments on a collective basis", if the potential participants "have no history of adequate communication and may represent diverse backgrounds with respect to experience or expertise", if "[m]ore individuals are needed than can effectively interact in a face-to-face exchange" or "[t]ime and cost make frequent group meetings infeasible", if there are severe disagreements among the individuals who shall interact so that "the communication process must be refereed and / or anonymity assured" and, finally, if "[t]he heterogeneity of the participants must be preserved to assure validity of the results, i.e., avoidance of domination by quantity or by strength of personality ('bandwagon effect')."

A panel in a Delphi study does not represent a numeric sample of a given population of experts, but a sample of available expertise. Pill (1971, p. 62) underlines that heterogeneity of the panel shall minimize "the possibility of overlooking some obvious facet of a question". While random sampling may be used in "wide-ranging, social and marketing Delphi studies", purposive sampling is required if depth and specificity of expertise is needed. (Day J & Bobeva M, 2005) To measure available expertise, Häder (2002) recommends to identify the number of perspectives to a topic, and to select one expert per perspective. Reported sample or panel sizes, as well as recommendations for optimal panel sizes in Delphi studies range from single-digit to four-digit numbers. (Akins et al., 2005; Mullen, 2003) In health applications, Delphi studies have been performed with four to 3000 participants. (Mullen, 2003) Turoff (1970) suggests 10 to fifty participants for a

[59] Sackman (1975) criticizes both the use of the term "expert" as well as "panel" in the context of Delphi surveys, arguing, firstly, that Delphi investigators have failed to present proof of statistical difference between experts and non-expert (p. 43), and secondly, that a panel requires a direct interaction between panelist; as this is not the case in anonymous Delphi exercise, the appropriate terminology would be "respondent". (p. 51)

Policy Delphi. Homogeneity of the level of expertise has been identified as a decisive factor for the validity of a Delphi survey's outcome. In a methodological analysis on adequate panel sizes for Delphi surveys, Akins et al. (2005) applied bootstrap sampling to a first round of responses from 23 participants. The raw data of the original participants were augmented to two computer-generated samples of 1000 and 2000 resampling iterations. Having compared the augmented results with the original responses, the authors concluded that "[p]anels of similarly trained experts (who possess a general understanding in the field of interest) provide effective and reliable utilization of a small sample from a limited number of experts in a field of study to develop reliable criteria that inform judgment and support effective decision-making." (Akins et al., 2005) Homogeneity of the level of expertise is also critical against the background that the selected experts must perceive each other as authoritative and credible. Assuring panelists that they are part of a peer-group is decisive for their readiness to re-think their opinion. (Häder, 2002)

The criteria which are applied to the selection of panel members in Delphi exercises depend on the type of the Delphi design, and range from screening procedures to determine an individual's expertise to using scales to identify the potential experts' degree of dogmatism as an indicator for their ability and willingness to change their opinion. Häder (2002) recommends to consider, but not to generalize such criteria. Pre-Delphi-Studies can be conducted to recruit experts and to determine their expertise and willingness to participate in the exercise. Häder (2000) found few publications, however, to prove that such additional effort was merited. As a prerequisite for participation in an expert panel, the panelists should have sufficient expertise in the topic which is being researched; furthermore, there should be a reasonable balance between industry and academia, and between regions. (Häder, 2000; Häder, 2002; cf. a. Pill, 1971)

The number of rounds for a Delphi survey depends of the goal of the exercise and on the definition of its endpoint. Häder (2002) distinguishes the following four types of Delphi surveys with different objectives:

- the purely qualitative survey, which serves to gather experts' ideas on a particular problem (type 1);

- the survey which uses qualitative and quantitative data to firm up a vague subject-matter and to forecast specific developments; the results of the survey are compared with actual developments (type 2);

- the survey which uses qualitative and quantitative data to collect and quantify experts' opinions (type 3) and

- the purely quantitative survey which aims to reach consensus among experts (type 4)

While one round of survey may suffice for a Delphi survey which strives to gather experts' ideas, several rounds will be required to reach consensus. Recommendations range from an open-ended first round with only one further round (Gallagher et al. 1996; Butterworth et al. 1995 in Mullen, 2003) to four or five rounds for the Policy Delphi. (Linstone & Turoff, 2002) A Delphi survey may be terminated upon consensus among participating experts, or at the point when the analysis of responses shows no significant variation from a previous round (stability).[60] The amount of information retrieved from a Delphi panel which remains consistent in size for four to five rounds is certainly substantial; however, two or three rounds may be sufficient and avoid increasing attrition. Walker & Selfe (1996, in Mullen, 2003) recommend to aim for a response rate of 70%. It has been observed that drop-out rates are highly dependent on the quality of the project design and on properly estimating and communicating the time and workload for the respondents. (de Meyrick, 2003) Drop-out rates have been shown to increase with panel size, while panels of 20 tend to keep their members. (Reid, 1988, in Mullen, 2003)

A characteristic element of Delphi surveys are feedbacks. With each new round of survey, the panelists receive the results of the previous round. Feedbacks take the form of graphic illustration (graphs, dots), tables or verbal comments, depending on

[60] Linstone, as cited by Day J & Bobeva M (2005), „suggests that marginal changes of less than 15% offer a working definition of a threshold for stability, which might be used as a criterion for termination of the Delphi exercise." (p. 106)

the type of data gathered, and on the goal of the study. Forecasting studies, which involve estimations of time intervals, mostly use numeric values, while questions geared at evaluating developments or scenarios, or which solicit verbal statements, also apply qualitative methods. (Mullen, 2003) De Meyrick (2003) identified 33 different statistical methods applied in Delphi studies. Most commonly used are mean, median, standard deviations, chi square, quartiles or interquartile ranges as well as percentages. (Mullen, 2003) Some experts on the method strongly oppose the exclusion of extreme opinions during feedbacks, arguing that it may lead to false consensus, since the "'pull of the median' is much stronger than the pull of the true". (Dalkey, 1969, p. 424) The use of the mean is not discouraged, though; Häder (2002) suggests to use standard deviations to measure the distribution of responses, and the arithmetic mean for tendency. Frequency distributions may complement the feedback to ensure that no information is lost and opposing views are maintained and visible. (McKenna (1994) and Mullen et al. (2000) in Mullen (2003)

In summary, key features of Delphi designs are:

- anonymity
- a structured flow of information through the
    - use of questionnaires
    - calculation of statistical group answers and
    - feedback to participants about the results of previous rounds
- several rounds of survey and
- a definition of end points.

4.2.2 The Policy Delphi

The Policy Delphi was introduced in 1969 and aimed to support decision-finding in committee processes. (Turoff, 2002) It was described as "an organized method for correlating views and information pertaining to a specific policy area and for allowing the respondents representing such views and information the opportunity to reaction to and assess differing viewpoints." (Ibid, p. 83) While previous Delphi surveys had focused on technology forecasts, and striven to achieve consensus among homogenous groups of experts, the Policy Delphi aimed to gather opposing views, to ensure that all relevant aspects of a topic under consideration are taken into account, that impacts and consequences are analyzed, and that the acceptability of a proposed policy option be examined. (Ibid, p. 83) Turoff had observed that "[i]n an atmosphere of budget cuts, belt tightening, and competition for limited funds, it may appear advantageous not to advocate, not to be noticed, and especially not to be held accountable for views, promises, or positions which require effort to document or substantiate". Furthermore, he found that "psychological characteristics of committee processes" such as "

- domineering personalities
- the unwillingness of individuals to take a position on an issue before all facts are in or before it is known which way the majority is headed
- reluctance to publicly contradict […] individuals in higher positions
- reluctance to abandon a position once it is publicly taken as well as
- fear of bringing up an uncertain idea that might turn out to be idiotic and result in a loss of face"

called for "substitutes for the committee process[…]". (Ibid, p.82) The Policy Delphi is based on the concept of the anonymous Delphi process, yet its objective is not to generate a decision or a consensus (even though a consensus may be reached during the exercise), but to present to a decision-maker a comprehensive range of options, along with the supporting evidence. A Policy Delphi can also function as a precursor to a consensus-oriented Delphi exercise, whereby the Policy Delphi

serves to gather relevant options for a subsequent consensus study. (de Meyrick, 2003) The course and outcome of an "honest" Policy Delphi, according to Turoff, cannot be predicted. (Turoff, 2002, p. 96)

Turoff recommends that a Policy Delphi be conducted in five rounds which shall cover the following six phases:

- Formulation of the issue
- Exposing the options
- Determining initial positions on the issues
- Exploring and obtaining reasons for disagreement
- Evaluating the underlying reasons
- Reevaluating the options

The process can be reduced to three rounds, if the research team formulates obvious issues for the first round. The respondents will add to the initial range of items and be asked for positions on an item and for underlying assumptions in the first round. (Ibid, p. 84) The issues at stake are rated according to desirability, feasibility, importance and confidence. Each item is ranked on a scale of four. (Table 4-1) Instead of including a neutral position in the rating scales, which is said to offer very little information, it is recommended that the respondents be given the opportunity to mark a 'no judgment-option'.

Table 4-1 Policy Delphi – Rating categories

Desirability (Effectiveness or Benefits)	
Very Desirable	- Will have a positive effect and little or no negative effect - extremely beneficial - justifiable on its own merit
Desirable	- will have a positive effect and little or no negative effect - beneficial - justifiable as a by-product or in conjunction with other items
Undesirable	- will have a negative effect - harmful - may be justified only as a by -product of a very desirable item, not justified as a by -product of a desirable item
Very Undesirable	- will have a major negative effect - extremely harmful - not justifiable
Feasibility (Practicality)	
Definitely Feasible	- no hindrance to implementation - no R&D required - no political roadblocks - acceptable to the public
Possibly Feasible	- some indication this is implementable - some R&D still required - further consideration or preparation to be given to political or public reaction
Possible Unfeasible	- some indication this is unworkable - significant unanswered questions
Definitely Unfeasible	- all indications are negative - unworkable - cannot be implemented
Importance (Priority or Relevance)	
Very Important	- a most relevant point - first-order priority - has direct bearing on major issues - must be resolved, dealt with, or treated
Important	- is relevant to the issue - second-order priority - significant impact but not until other items are treated - does not have to be fully resolved
Slightly Important	- insignificantly relevant - third-order priority - has little importance - not a determining factor to major issue
Unimportant	- no priority - no relevance - no measurable effect - should be dropped as an item to consider

Confidence (In Validity of Argument or Premise)	
Certain	- low risk of being wrong - decision based upon this will not be wrong because of this "fact" - most inferences drawn from this will be true
Reliable	- some risk of being wrong - willing to make a decision based on this but recognizing some chance of error - some incorrect inferences can be drawn
Risky	- substantial risk of being wrong - not willing to make a decision based on this alone - many incorrect inferences can be drawn
Unreliable	- great risk of being wrong - of no use as a decision basis

(The table is reproduced from Turoff, 2002, p. 86-87)

The term 'expert' is not considered the most appropriate label for the respondent in a Policy Delphi, since "a policy issue is one for which there are not experts, only informed advocates and referees. […] The expert becomes an advocate for effectiveness or efficiency and must compete with the advocates for concerned interest groups within the society or organization involved with the issue." (Ibid, p. 80) Hence, a Policy Delphi may also become a "self-fulfilling prophecy", if the respondents are at the same time involved in decision-making processes for the subject under consideration. (de Meyrick, 2003) Several pitfalls have been identified for conventional Delphis (Linstone & Turoff, 2002), of which some may also apply to Policy Delphi. Among these are an over-reduction of complexity, illusory expertise (meaning that experts are blind for other views outside of their field of expertise), or careless execution of the survey (both by the researcher and the participant) (de Meyrick, 2003). Regarding the size of a panel, Turoff recommends that "[…] in many policy areas, a larger number of respondents, in the area of twenty or more, is commensurate with the number of differing interests that must often be considered in the increasingly complex issues facing organizations." (Turoff, 2002, p. 83)

Guidelines for the conduct of a Policy Delphi recommend *i.a.* at least two professionals to design / monitor the exercise, sometimes prior development of scenarios, factual summaries of background information, pre-tests, presenting respondents their original vote during feedbacks, as well as ensuring that the panel represents a peer group. (Ibid, p. 88-89) It is highly recommended to explore

dissensions when analyzing the results of a Policy Delphi. Aggregated responses of different groups of respondents (e.g. groups representing different stakeholders) will enable the researcher to identify trends among groups. (Ibid, p. 96). The ideal approach to test the reliability of the results would be to establish parallel panels, or to test-retest a panel. De Meyrick (2003), however, found only one project that had realized this approach.

The issue of promoting R&D for neglected diseases is debated in various fora and by stakeholders from different professional backgrounds and affiliations in developing, developed and threshold countries. The aim of our research project was to complement current debates with quantifiable data. Against the background of the possibilities and objectives outlined above for Delphi and Policy Delphi exercises, we considered a Policy Delphi to be the suitable method to collect the data for our research question.

4.3 Data Analysis

4.3.1 Quantitative data

Since the panel of our Policy Delphi survey was not a representative sample of a population of experts, planned analyses included descriptive, but not inferential statistics. (cf. a. Häder, 2000, p. 7 ff.) To inform the participants of the results of the categorical items after each round of the survey, frequency analysis would be performed, and the percentage scores would be displayed in bar charts. For the purpose of the feedback, frequency analysis were based on fully completed questionnaires only. (cf. Chapter 4.2.1, *Feedback*) In the final analysis of the survey data (cf. Chapter 5, *Results*), frequency analysis also included questionnaires that had been partially completed.

In the set of raw data, missing values were coded differently depending on whether the respondent had not seen the question, *i.a.* because of abandoning the questionnaire (Code -77), or whether he or she saw the question, but did not answer it (Code 0); in the final analysis, both types of missing values were summarized to form a single category labeled “missing data”. Cross-tabulations using break variables of the questionnaire section on demography (professional affiliations / place of residence of the participants) were performed for selected variables to

identify variations between subgroups of survey respondents. Standard deviations and mean values reflected the overall support for an item and the degree of consensus among the respondents. The respondents were asked to rank categorical items on scales of four, with a fifth option being labeled “no judgment”. (cf. Chapter 4.4.1 including *questionnaire development*) The value labels ranged from “1” for the most positive replies to “4” for the most negative reply. The value label for the answer “no judgment” was “5”. No judgment-replies were considered active replies and were not coded as missing values. The results for no judgment-replies were included in the frequency analysis as a source of information; however, they were excluded from calculations of standard deviations and mean values.

4.3.2 Qualitative data

A Policy Delphi may include general comments or full-text replies, i.e. additions or modifications of questionnaire items. Often, these are quite numerous, and the researcher faces the challenge to develop a manageable questionnaire for the second round, while taking due account of the contributions made by the respondents. (cf. de Villiers et al., 2005) We asked the respondents to provide comments on the survey and to modify or complement existing items; for the latter option, each respondent could add a maximum of three suggestions for modifications and / or additions. Comment fields were cleaned from information which could reveal the authorship, and forwarded to the respondents with the feedback. Full-text fields that contained suggestions for modifications of, or additions to, existing items were subject to a qualitative analysis with a view to incorporating these suggestions into the questionnaire for the second round. The method chosen for the qualitative analysis was the “text sorting technique” (TST) which recommends the following steps (for this and the following cf. Beywl & Schepp-Winter, 2000, p. 62 ff.):

- Coding of questionnaires / respondents
- Include text in a word document
- Separate texts into meaningful units and check them against the research question
- Development of categories
- Document the edited text passages
- Development of brief descriptions for categories.

To prepare for the data analysis, numeric codes are assigned to each questionnaire or respondent and to each full-text questionnaire item. It is recommended that the codes are preceded by special characters to perform search and sorting operations. The qualitative data are organized in columns (Word or Excel format) under the headings of the respondent's questionnaire code, the questionnaire item number, the variable name and the value, i.e. the full-text response. The last column heading is labeled "category" and contains the three-digit number of the category (or categories) to which the full-text response is being assigned. (Table 4-2)

Table 4-2 Organization of qualitative data for category development

Respondent ID	Questionnaire Item	Variable name	Value	Category
000	000	XXX	Full-text response	000

Referring to Kelle / Kluge (1999) and Kleining (1994), Beywl / Schepp-Winter (2000, p. 66 ff.) suggest a process of iterative / repeated reading of all incoming suggestions for the development of categories, and the identification of similarities. This process shall always be guided by the question whether the newly developed category serves to answer the original question. Categories shall not overlap, and dichotomies (good-bad) or categories headed 'miscellaneous / other' are to be avoided. In an ideal category system, the maximum number of categories that are assigned to each original questionnaire item ranges between three and eight. The number of responses in each category shall not exceed 30, whereby one response can be given various category codes. Categories can be subdivided, but subdivisions should not exceed three levels. Each category is to be documented in a legend. Categories may include in-vivo-codes (exact wording of a respondent) or codes developed independently from the respondents' wording. After the categorization for a questionnaire item is complete, the full-text replies are sorted by category to check the validity of the coding concept.

4.4 Implementation of the Policy Delphi Survey

The survey was designed along the guidelines described in Chapter 4.2.2, with slight adaptations to the recommended structure to minimize attrition rates, and to accommodate the research question. Sections 4.4.1 ff. below describe the design and the implementation of the survey. The survey was conceptualized as an online exercise using Unipark, the university version of Globalpark EFS Survey[61]. Unipark EFS Survey works with all common browsers; no software installation is required to design a survey or to participate in it. In addition to enabling online questionnaire design and survey implementation, the software facilitates mailings to survey participants, generates personalized access codes, online data analysis, online reports and data exports in different formats. Separated exports of participants' personal data (names, e-mail addresses) and survey results ensure anonymous data analysis.

4.4.1 Step 1: Literature review, questionnaire development, panel selection

LITERATURE REVIEW

Prior to the development of the questionnaire for the first round, a literature search was performed using the internet search function of the literature data base Reference Manager, Version 11.0[62] (s. Annex II – Survey Documentation). In addition, documents and grey literature were researched and retrieved by keyword search using the Google search engine, or from relevant homepages (e.g. WHO, EMA). Publications of an exclusively clinical character, e.g. case reports, were eliminated from the search results. Publications which were considered appropriate dealt with political, ethical, legal / regulatory and / or economic aspects of orphan and neglected diseases. The literature was reviewed against the backdrop of the following questions:

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[61] The survey was conducted with Unipark Version 5.2.

[62] Reference Manager searches the ISI Web of Science, a selection of Web of Science databases, PubMed, the National Library of Medicine's public access database, and Z39.50 sites, a selection of Z39.50 databases.

- Which are the likely causes for a treatment deficit for neglected diseases?
- Which measures should / could be taken to remedy this deficit?
- Should a regulatory instrument be created to promote neglected disease R&D?
- How could neglected diseases be defined (with a view to developing a regulatory instrument)?
- Are orphan drug laws and their provisions an effective measure to foster R&D for rare diseases?
- Could orphan drug laws and their provisions serve as a blueprint for measures to foster R&D for neglected diseases?
- How desirable and how feasible are the provisions proposed in the draft Medical Research and Development Treaty for the promotion of neglected disease R&D?

QUESTIONNAIRE DEVELOPMENT

Along the lines of the above questions, the items for the first round of survey were formulated and organized into chapters on causes for the treatment deficit, on the performance of orphan drug regulations for rare diseases, on measures to promote R&D for neglected diseases, on criteria to define neglected diseases and on the option of a regulatory instrument to promote R&D into neglected diseases. The survey closed with a chapter in which the respondents were asked to contribute information on their professional background, their professional affiliation and their place of residence. In view of the fact that there would be only two rounds of survey, it was decided to ask the respondents in the first round to rank pre-formulated items, and to suggest modifications and additional items. To this end, three full-text fields each were included in Chapters I (Causes for the treatment deficit for neglected diseases), III.1 (Measures to foster R&D for neglected diseases), III.5 (Criteria for a definition of neglected diseases) and IV. 2 a) and b) (Demographic data on professional backgrounds and professional affiliations of

survey respondents).[63] The questionnaire was first drafted as a paper version and then developed as online-questionnaire in the EFS software.

Different scales were selected for the various chapters of the survey. Causes were to be rated according to importance, and orphan drug regulations and their provisions according to effectiveness. Measures to promote R&D into neglected diseases were rated according to desirability and to feasibility; the same scale was used for the question on a regulatory instrument to promote R&D into neglected diseases. In the first round of survey, the experts were also asked to name three criteria each for a definition of neglected diseases. In the last chapter, multiple choices were possible for the question on professional backgrounds; one option each could be selected for the questions on professional affiliations and place of residence. The questions on professional backgrounds and affiliations contained an 'other'-option with a full-text field. Entries into these full-text entries would be included in the list of options in the second round of the survey. Full-text fields for comments were included in the section on the desirability and feasibility of a regulatory instrument for neglected diseases, and as general comment field at the end of the survey.

The labels for the variables were:

1= most important / very desirable / definitely feasible[64] / very effective

2= important / desirable / possibly feasible / effective

3= unimportant / undesirable / possibly unfeasible / ineffective

4= least important / very undesirable / definitely unfeasible / very ineffective

5= no judgment

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[63] Chapter II on the effectiveness of orphan drug regulations for rare diseases served to inform the research team how familiar the respondents were with orphan drug-incentives and whether they considered them effective for rare diseases. However, since our research project did not aim to identify new options to foster R&D for rare diseases, the Chapter was not repeated, and no additions and modifications were requested. Orphan drug-style incentives were, however, part of the list of measure to promote R&D into neglected diseases. (Chapter III)

[64] In round one, the ranking said "very feasible – feasible- unfeasible - very unfeasible" while the definition read "definitely feasible – possibly feasible – possibly unfeasible - definitely unfeasible". This was corrected in the second round.

The no-judgment-option was given instead of a "neutral" position to enable the participants to actively indicate that they did not wish to express an opinion on an item. Prior to launching the survey, a pre-test via the EFS survey software was carried out during which five individuals of different academic backgrounds and professional affiliations contributed 21 technical and editorial comments on the survey design, the formulation of the items and on the implementation of the online version.

PANEL SELECTION

The participants were selected from the following sources:

- Publications on neglected and orphan diseases

- Participants in the Conference on Neglected Infectious Diseases, organized by the DG Research of the European Commission, Brussels, November 8 and 9, 2006, which the author attended (http://ec.europa.eu/research/health/infectious-diseases/neglected-diseases/pdf/nid-conference-final-report052007_en.pdf)

- Contributions to two online hearings (November 1-15, 2006 and August 15 – September 30, 2007) of the WHO Intergovernmental Working Group (WHO-IGWG) to develop a global strategy and plan of action for neglected diseases (http://www.who.int/phi/public_hearings/en/)

- A letter signed by 162 scientists, public health experts, lawyers, economists, government representatives and parliamentarians to accompany the submission of the draft Medical Research and Development Treaty to the WHO Commission on Intellectual Property, Innovation and Public Health in 2005.

The selection was purposive insofar as we chose sources that would ensure that the invitees were interested in the matter, knowledgeable of the matter, and would represent a broad professional and geographic spectrum. When selecting the panel, however, we could only assume the participants professional background or affiliation, or their place of residence. Since it was impossible to predict

participation and attrition rates at the onset of the study, we did not reduce or adjust the potential panel to achieve a balanced sample for geographic distribution, professional backgrounds or professional affiliation. The outcome of the demography section of the survey would later have to show whether the data would lend themselves to a stratification of the experts, and to cross-tabulations of the results.

4.4.2 Step 2: First round of the survey

Contact data[65] that were available from the aforementioned publications, hearings and conference proceedings were entered into an Excel sheet. To invite potential participants, first names, last names and Email addresses were imported into the EFS survey software. The software generated participants IDs and personalized access codes to the survey. An Email invitation was sent out on March 9, 2008 which included the personalized access code to the survey, and a brief project description. Two weeks into the field time, a reminder Email was sent to all participants who had activated the link to the survey, but who had not completed the questionnaire (the invitation and related documents are reproduced in the Annex to this document). At the request of several participants, the closing date for the first round was extended from March 29 to April 3, 2008.

4.4.3 Step 3: Analysis of the data of the first round, revision of the questionnaire

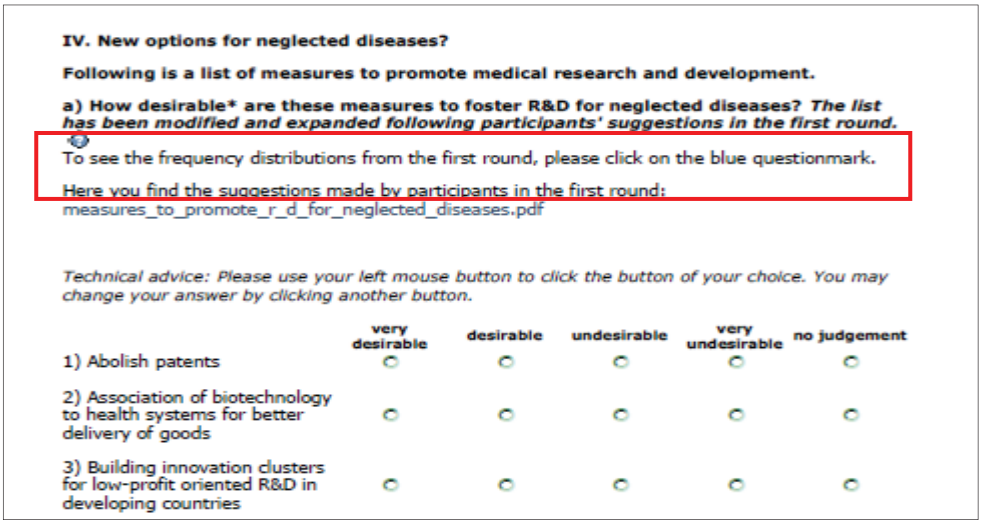
ANALYSIS OF THE DATA OF THE FIRST ROUND

Feedbacks in our survey served two purposes: a) to forward the quantitative results of the first round to the participants and b) to display the suggestions and comments received during the previous round. The respondents were not shown their votes from the previous round, though, as this would have required that the author sign a data protection waiver in order to receive a combined data export of survey results and contact data; the anonymity of the experts vis-à-vis the research team would thus have been lifted, which we considered a breach of our initial commitment to

[65] Contact data included last names, first names, Email addresses, and, if available, information on professional background, professional affiliation and country of residence.

anonymity. Quantitative data of the first round were analyzed using the Globalpark Reporting function as well as SPSS and Microsoft Excel in their current versions. Frequency distributions of categorical variables were prepared and displayed in bar charts. Frequencies were calculated for all participants who fully completed the questionnaire for the first round (N=117). To feed back the raw data of the full-text fields (suggestions and modifications), the contents were edited, and information which revealed a respondent's identity, such as names, contact data or links to proper publications were removed. The contents were then collated in pdf-documents. Links to both the bar charts and to the pdf-files were included in the relevant pages of the questionnaire for the second round. (Fig. 4-1, Fig. 4-2)

Fig. 4-1 Screenshot: Access to the feedback of the 1st Round (Frequencies)



IV. New options for neglected diseases?

Following is a list of measures to promote medical research and development.

a) How desirable* are these measures to foster R&D for neglected diseases? *The list has been modified and expanded following participants' suggestions in the first round.*

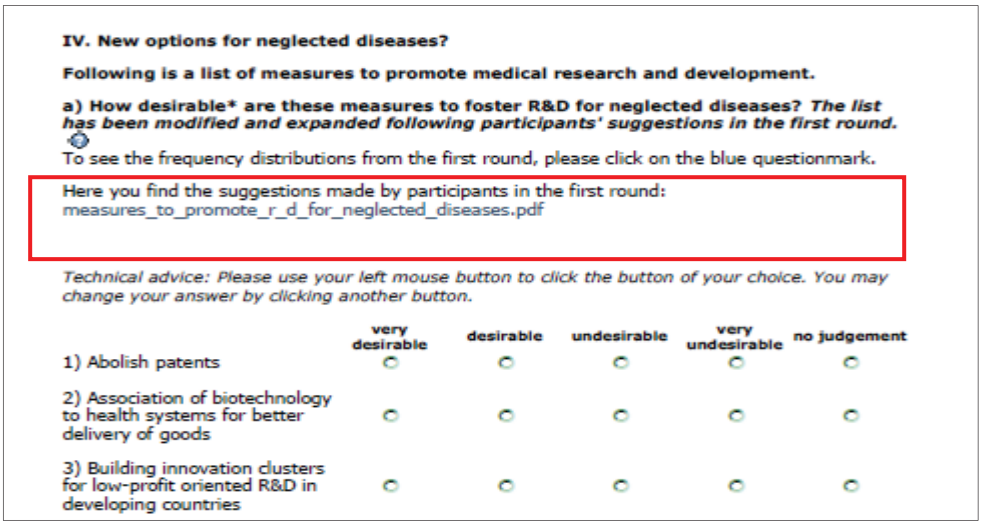
To see the frequency distributions from the first round, please click on the blue questionmark.

Here you find the suggestions made by participants in the first round:
measures_to_promote_r_d_for_neglected_diseases.pdf

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	very desirable	desirable	undesirable	very undesirable	no judgement
1) Abolish patents	○	○	○	○	○
2) Association of biotechnology to health systems for better delivery of goods	○	○	○	○	○
3) Building innovation clusters for low-profit oriented R&D in developing countries	○	○	○	○	○

Fig. 4-2 Screenshot: Access to the feedback of the 1st Round (Full-text replies)



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Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	very desirable	desirable	undesirable	very undesirable	no judgement
1) Abolish patents	○	○	○	○	○
2) Association of biotechnology to health systems for better delivery of goods	○	○	○	○	○
3) Building innovation clusters for low-profit oriented R&D in developing countries	○	○	○	○	○

REVISION OF THE QUESTIONNAIRE

The questionnaire for the first round contained two types of full-text responses, i.e. comments and suggestions for new items / modifications of existing items. The latter, suggestions and modifications, formed the basis for the revision of the questionnaire. To keep the questionnaire for the second round manageable, the suggestions were clustered and aggregated using the TST-method described in Chapter 4.3.2. Utmost effort was devoted to the analysis of the numerous suggestions and modifications, which were matched with existing items, or formed into new items. The process is described below.

All full-text responses (excluding those in the comment sections) were exported from the EFS survey software into an Excel file. The data for each chapter (causes for the treatment deficit, measures to promote R&D for neglected diseases, criteria for a definition of neglected diseases) were saved in separate work sheets. The data were organized into six columns (Table 4-3).

Table 4-3 Qualitative data analysis: Example of structuring of data

Questionnaire No.	varname	Question Code	value	Category	corresponding existing/ newly created item no.
§825	Addmeas3	#06	to mobilise fund	100	*e.g. previous questionnaire item no.xyz*
§829	Addmeas3	#06	Commitment & accountability of organization receiving funding towards achievement of goals	100	
§837	Addmeas2	#05	Availability of adequate funding	100	
§861	Addmeas2	#05	it has to go through taxes and public funding; tax reduction to companies can never be a 'lasting' commitment, the research program will be cut as soon as the company realizes that it is lost money.	100	
§873	Addmeas2	#05	Commitment from governments in developed countries to fund R&D	100	
§878	Addmeas3	#06	Follow up of tho ongoing program	100	
§894	Addmeas1	#04	calls from international R&D org. like EC for research projects	100	
§911	Addmeas2	#05	public accountability systems for producers and providers	100	
§920	Addmeas1	#04	Increase fundings opportunities for neglected tropical diseases	100	
§924	Addmeas3	#06	more available grant for R and D for neglected diseases	100	
§971	Addmeas1	#04	More predictable and sustained funding for PPPs e.g. MMV	100	

Export and coding of qualitative data: Table 4-3 shows suggestions for additional items that were received in the first survey round for the questionnaire heading “Measures to promote research and development for neglected diseases”. Each participant was allowed to make a maximum of three suggestions which, for the purpose of the qualitative analysis, were coded as question 04, 05 and 06. The above suggestions were, after qualitative analysis, included in a Category 100 labeled “Measures relating to increased / more sustainable funding and to accountability for funds received”. Some entries, such as the one shown for questionnaire no. §861 above, contained not only additions or modification of existing questionnaire items, but also comments on selected item in the list of measures, (here: tax reduction/tax credits).

The first column in the Excel work sheets, headed Questionnaire No., contained the three-digit ID which the EFS software generated for each survey participant. For search and grouping purposes, the EFS codes were preceded by the character "§". The second column contained the variable name (here: AddMeas1-3, which abbreviates the three full-text fields for suggestions in the chapter on measures to promote R&D into neglected diseases). In addition to the variable name, a third column (Question code) contained a code which was assigned to each variable and which was preceded with the special character "#"; full-text fields in the questionnaire were thus numbered chronologically, irrespective of their original number in the questionnaire. The fourth column contained the full text replies of the respondents, while the fifth column had the number of the category which was assigned to the full-text reply. Full-text replies that contained several suggestions, or whose content could be matched with more than one category heading could be grouped into several categories. In a sixth column, the full-text replies were either cross-referenced with previous questionnaire items, or assigned new item numbers. For each questionnaire section, a system of categories was developed *ad hoc*. Original wording was retained in those cases where suggestions were very specific and could not be merged with other statements. Full-text entries were compared and analyzed with a view to identifying patterns and structures in the data that would eventually serve as new category or subcategory. (cf. Kelle Udo & Kluge Susanne, 1999, p. 54 ff.) The procedure for each questionnaire chapter is described below.

CAUSES FOR THE TREATMENT DEFICIT FOR NEGLECTED DISEASES

Chapter I of the questionnaire for the first round of survey contained seven likely causes for the deficit in treatment for neglected diseases. The experts contributed 98 suggestions to this section which, in a first step, were clustered into eight categories. (Table 4-4)

Table 4-4 Category legend: Causes for the deficit in treatments for neglected diseases

Category Legend: 'Causes for the Treatment Deficit'.*	
000 (9)	Comment or proposal how to improve the situation
100 (9)	Causes relating to poverty
200 (15)	Causes relating to structural (delivery / health system structures) or policy deficits in developing (endemic) countries
300 (12)	Causes relating to inadequacy of current incentives
400 (3)	Causes relating to inadequate prevention
500 (9)	Causes relating to human resources / education / training in developing countries
600 (11)	Causes relating to lack of awareness / advocacy
700 (9)	Causes relating to disease-specific research difficulties
800 (20)	Causes relating to inadequate policy / insufficient (financial) commitment / inadequate research priorities
900 (4)	Causes relating to inadequate research coordination / cooperation
999 (3)	not applicable to the question

** Three-digit-numbers labeled the categories while the numbers in brackets show the number of suggestions that were included in a category. Where necessary, two categories 000 and 999 were established. Comments (000) gathered contributions and statements that could not be identified as a cause. At the request of the respondents, a comment field was added to this section in the second round of the survey. The category 999 (not applicable to the question) included full-text entries such as contact data.*

In a second step, eight new items were extracted from these categories, and several suggestions were matched with original items from the first round of survey. Table 4-5 illustrates the modification and expansion of items in Chapter I.

Table 4-5 Identical and new questionnaire items (Causes for the treatment deficit)

Identical items in round one and two	Newly added items in round two
No or inadequate direct public funding for research and development (R&D) for neglected diseases	Disease-specific research difficulties (unknown etiology, lack of research material)
No or inadequate private sector investment into R&D for neglected diseases	Inadequate research priorities in private sector R&D
No or inadequate incentives for the private sector to invest into R&D for neglected diseases	Lack of awareness / visibility of neglected diseases
No or insufficient sustainability of public funding for R&D for neglected diseases	Lack of health-needs driven priority setting in public funding
No or ineffective drugs for neglected diseases	No or inadequate research coordination
No or inadequate access to effective drugs for neglected diseases	No or inadequate health delivery infrastructure and staff in developing countries
No or inadequate research infrastructure in countries with neglected diseases	Poverty as disease-proliferating factor (*i.a.* inadequate prevention, inadequate housing, lack of clean water) in endemic countries
	Poverty as reason for market failure (perception of no market for drugs, insufficient R&D)

Following the same procedure, eight categories were developed for the 134 suggestions which the experts offered for the section on measures to promote research and development into neglected diseases (Table 4-6)

Table 4-6 Category legend: Measures to promote R&D for neglected diseases

Category No.	**Category title**
000 (5)	Comment
100 (11)	Measures relating to increased / more sustainable funding and to accountability for funds received
200 (19)	Measures relating to enhancing research cooperation, incl. interdisciplinary cooperation (with *i.a.* veterinary medicine, traditional medicine, epidemiology)
300 (26)	Measures relating to capacity building in and knowledge transfer to endemic (developing) countries
400 (3)	Measures relating to improving access to health care and to drugs
500 (17)	Measures relating to funding priorities
600 (24)	Measures relating to advocacy and increasing visibility / awareness of ND
700 (12)	Measures relating to incentives for and encouragement of the private sector
800 (23)	Measures relating to structural reforms / further development of current regulations

Since the suggestions in this section were far more heterogeneous than those in Chapter I on the causes for the treatment deficit, 36 new items were extracted. Together with seven previous and seven modified items from the first round, the list of potential measures to promote R&D into neglected diseases increased from 16 to the 50 items.

Table 4-7 below reproduces the list of items which were repeated in the second round, either with unchanged or modified wording, Table 4-8 shows the newly included items.

Table 4-7 Identical and modified questionnaire items (Measures to promote R&D)

Identical items in round one and two	**Modified items (the wording in italic print is that of the second round)**
Exemption of drugs from market exclusivity	Advance market commitments *(Incentives for the private sector (e.g. advance market commitments, governmental incentives))*
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	Existing patent regulations *(Existing patent regulations (e.g. WTO-TRIPS, Doha-Declaration))*
Market exclusivity	Investment obligations into neglected diseases for drug producers / sellers *(Obligation for the private sector to invest x % of profit made from other drugs / treatments into neglected diseases)*
Obligations for national governments to invest into neglected disease R&D	Patent pools *(Patent pools / more flexible patent laws to improve access to research tools)*
Open source regulations (e.g. for scientific data / compound libraries)	Prize funds for drug innovation *(Prize funds with prizes awarded based on degree of innovation)*
Public-private partnerships	Protocol assistance *(Protocol and regulatory advice / assistance to neglected disease R&D projects)*
Separation of innovation incentives from drug prices	Tax credits *(Tax credits / tax incentives)*

Table 4-8 New questionnaire items (Measures to promote R&D)

New items in round two
○ Abolish patents
○ Association of biotechnology to health systems for better delivery of goods
○ Building innovation clusters for low-profit oriented R&D in developing countries
○ Building research, technical and regulatory capacity in developing countries
○ Competitive grants to publicly fund research
○ Contribution by foreign donors towards capacity building and strengthening the research infrastructure in developing countries
○ Development to phase III trials by public laboratories
○ Educate / inform the public about the individual and societal burden of disease of neglected diseases
○ Establishment of accountability systems for funds received
○ Establishment of an international health-needs driven R&D agenda matched to technological opportunities
○ Establishment of public (or affordable) preclinical research facilities
○ Exclusive funds for R&D / budgetary set-asides exclusively for purchasing medicines for neglected diseases
○ Global funders forum to set priorities
○ Government support and funds for multilateral efforts (e.g. WHO-TDR)
○ Include neglected diseases in university curricula

Table 4-8 continued

New items in round two
○ Interconnection between research projects on different neglected diseases
○ Interdisciplinary research cooperation with e.g. veterinary medicine, traditional medicine, epidemiology
○ International / transcontinental research cooperation involving researchers from developing countries
○ International regulations regarding the private sector
○ Link between neglected disease R&D and research and clinical care for priority diseases such as HIV, TB or Malaria
○ Lower private sector influence on R&D priority setting
○ Neglected disease R&D as priority in relevant European Union funding programs (e.g. FP7)
○ New alternative juridical instruments which allow governments to foster essential health research and development
○ Parallel measures to improve access to health care and medicines
○ Price increases (10-20%) for brand name drugs paid by public health programs to invest this profit in neglected disease R&D
○ Private donations to "real" pharmaceutical companies to develop drugs for neglected
○ Raise awareness among policy makers for the impact of neglected diseases on development
○ Raising the scientific profile of neglected disease research (better career / publication opportunities)
○ Reorganize intellectual property rights as intellectual monopoly privileges
○ Requirement for developing countries to include research with an adequate budget in all health programs
○ Royalty arrangements for the benefit of neglected disease R&D if private sector receives exclusive license on government-owned invention for any disease
○ Selective investment (as incentive) in companies which invest in neglected disease R&D
○ Sharing or transfer of technology to developing countries
○ Simplified / fast-track funding procedures
○ Treaty on cost-effectiveness of new health technologies linked to a competitive tender system
○ Voucher systems in developed markets (as with the FDA) for other products

CRITERIA FOR A DEFINITION OF "NEGLECTED DISEASES" IN A REGULATORY INSTRUMENT

In the first round of the survey, the participants were asked to suggest three criteria each which they deemed most relevant for a definition of neglected diseases. The section did not contain pre-formulated items, but three full-text fields. The number of suggestions made was considerable (237); similar to the first chapter on causes for the treatment deficit, however, they were rather homogenous. The suggestions were clustered into six categories (Table 4-9) from which six criteria for a definition

of neglected diseases were extracted. In the second round of the survey, the participants would be asked to rate these criteria according to importance.

Table 4-9 Category legend: Criteria for a definition of neglected diseases

Category No.	Category title
000 (7)	Comment
100 (72)	Criteria relating to absence of effective treatment and lack of ongoing research
200 (79)	Criteria relating to prevalence, burden of disease
300 (41)	Criteria relating to disease severity: life-threatening, serious, debilitating, chronic
400 (13)	Criteria relating to lack of access to existing effective treatment
500 (7)	Criteria relating to market failure / lack of purchasing power
600 (6)	Criteria relating to awareness / visibility of relevant diseases
999 (16)	Not applicable to question

4.4.4 Step 4: Second round of the survey including feedback

On July 10, 2008, the questionnaire for the second round was finalized and mailed to the 117 panelists who completed the survey of the first round. The number of items for the questions on causes for the treatment deficit and on measures to promote R&D increased considerably between round one and two; the item on the regulatory instrument remained unchanged, while the question on criteria for a definition of neglected diseases changed from full-text replies in the first round to a quantitative question in the second round. In the demography section, new answering options for professional affiliation and professional background had been added to include the panelists suggestions. Following requests from survey participants, comment fields had been added to all sections of the questionnaire in the second round. Table 4-10 below compares the structure of the questionnaires for the first and for the second round. (The questionnaires for both rounds are reproduced in the Annex to this document)

Table 4-10 Structure of the questionnaires for Round I and II

Type of Question	Question and no. of items	
	Round one	**Round two**
Closed-ended question / Likert Scale / full-text fields	**Causes for the treatment deficit for neglected diseases**	
	7 items plus 3 full-text fields to add items	15 items plus one comment field
Closed-ended question	**Familiarity with orphan drug acts**	not repeated in the second round, one full-text field provided to comment on the outcome displayed in the feedback
	3 options	
Closed-ended question / Likert Scale	**Effectiveness of orphan drug acts**	
Closed-ended question / Likert Scale	**Effectiveness of four key incentives in orphan drug acts**	
Closed-ended question / Likert Scale / full-text-fields	**Desirability & feasibility of measures to promote R&D for neglected diseases**	
	16 items plus 3 full-text fields to add items	50 items plus one comment field
Closed-ended question / Likert Scale	**Desirability & feasibility of a regulatory instrument to foster R&D for neglected diseases**	
	1 item plus two full-text fields for comments (one for desirability and feasibility each)	1 item plus one full-text field for comments
Full-text fields (Round One), Closed-ended question / Likert Scale (Round Two)	**Criteria for a definition of "neglected diseases"**	
	3 full-text-fields for suggested criteria	6 options plus one full-text field for comments
Full-text field	**Comment on the survey**	
Hybrid question, multiple answers were allowed	**Professional background**	
	5 options plus one full-text field for addition	8 options plus one full-text field for additions
Hybrid question	**Profession affiliation**	
	5 options plus one full-text field for additions	6 options plus one full-text field for additions
Closed-ended question	**Place of residence**	
	3 options	3 options

A brief welcoming note opened the survey on page one of the questionnaire; notes on the technical procedure followed on page two. The list of questions began on page three. As in the first round of the survey, all participants who activated the link to the questionnaire, but did not complete it, received a reminder Email. At the request of several participants, the deadline to fill in the questionnaire was extended from August 8, 2008 to August 15, 2008. Of the 114 experts whom we were able to contact for the second round (three Emails were undeliverable), 68% (n=77) activated the link to the questionnaire, and 49% (n=56) completed it.

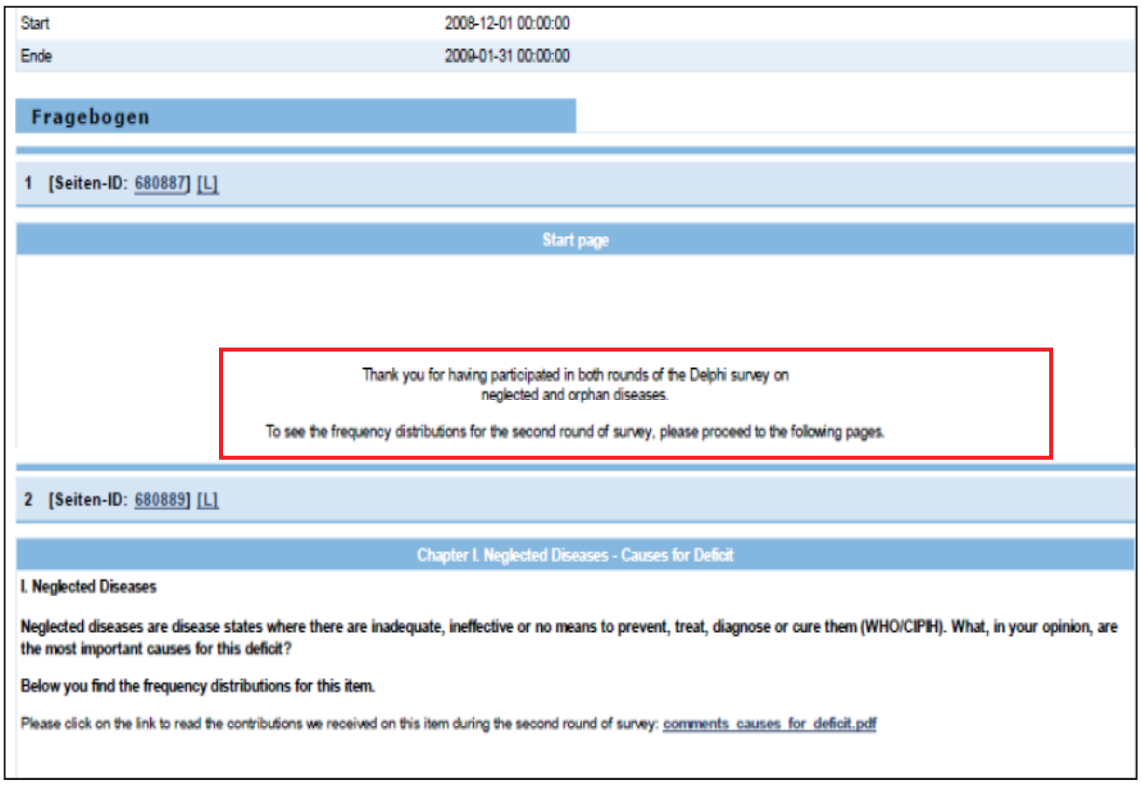
4.4.5 Step 5: Analysis of the second round data

After the closing date for the second round, frequency distributions were prepared for the considerably increased number of categorical variables, and displayed in bar charts. Frequencies were calculated for all participants who completed the questionnaire for the second round (N=56). Comments in full-text fields were edited to exclude information that revealed the author's identity, and collated in pdf-files.

4.4.6 Step 6: Second and final feedback

On December 1, 2008, a personalized link was mailed to the panelists with which they could access the survey platform and view the results of the second round of survey. (Fig. 4-3) Access to the second feedback was available until January 31, 2009. No requests to extend the access time beyond this date were received.

Fig. 4-3 Screenshot: Final feedback after the second round

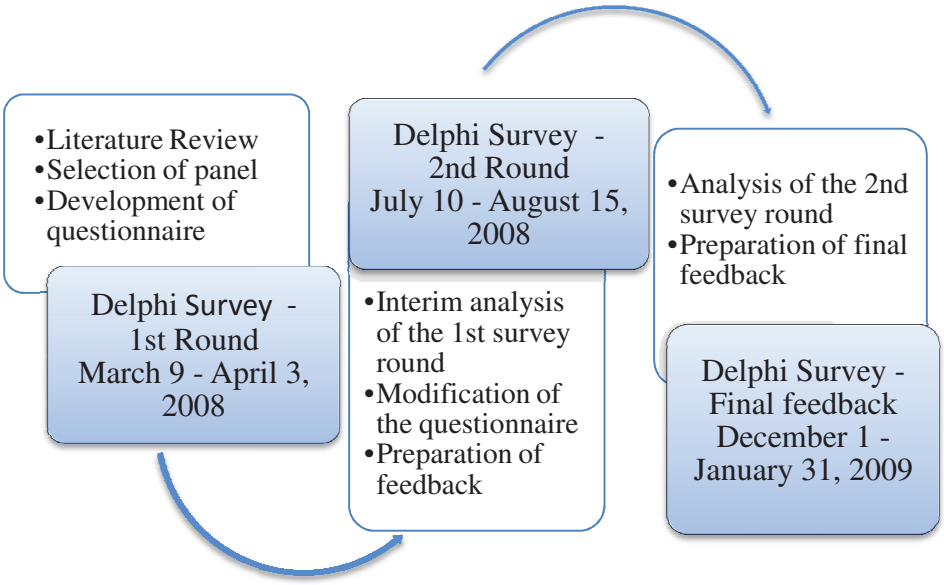


5 Results

5.1 Timeline, Participation and Attrition

The survey was conducted in two rounds over a period of nine months. The time given to fill-in the questionnaires was three and a half weeks for the first round (March 9 – April 3, 2008) and five weeks for the second round (July 10 – August 15, 2008). Access to the final feedback ended on January 31, 2009. The development and implementation of the survey encompassed six steps (Fig. 5-1) which have been described in detail in Chapter 4.4.

Fig. 5-1 Delphi Survey on promoting R&D into neglected diseases



The mean processing time (arithmetic mean) for the questionnaire was 18 minutes for the first round and 30 minutes for the second round, which exceeded the assumed processing time (10 minutes for the first round and 15-20 minutes for the second round).

Of the 388 experts we attempted to contact, 326 supposedly received the invitation. Of these, 47.7% (n=159) accessed the survey and 117 participants completed it. 114 participants received the invitation for the second round., and 56 participants completed the second round of the survey. Table 5-1 below details the participation and attrition rates of both rounds of the survey taking into consideration the number

of experts who activated the personalized access code to the survey (Net participation 1 and 2).

Table 5-1 Participation and Attrition

	Round One		**Round Two**	
	N	**%**	**N**	**%**
Total sample	388	100	117	100
Email undeliverable[66]	62	15.9	3	0.02
Adjusted total sample	**326**	100	114	100
Net participation (1)	159	47.7	77	67.5
Net participation (2)	159	100	77	100
Survey Completed	**117**	73.6	**56**	72.7
Survey Suspended	42	26.4	21	27.2

In the first round of the survey, the majority of the potential respondents who abandoned the questionnaire did so after having read the introductory page (n=12) or the first list of questions (n=15). In the second round, n=21 participants abandoned the questionnaire, n=8 of these prior to having accessed the first list of questions.

Of the total number of participants contacted, 84 had signed the accompanying letter to the draft Medical Research and Development Treaty. In both rounds of the survey, these signatories represented about 25% of the survey participants who completed the survey (n=28/round 1, n=14/round 2)

[66] A small number of Emails were rejected because the invitation was considered Spam mail. In these cases, the author re-sent the Email invitation from a different (personal) Email address.

5.2 The Questionnaire Items – Round I and II

For the purpose of the feedbacks in the course of the survey, frequency distributions had exclusively considered fully completed questionnaires, and had been based on N=117 for the first and N=56 for the second round. To benefit from answers by respondents who filled in only part of the questionnaires, frequency distributions for the final data analysis in this chapter are based on N=159 for the first and N=77 for the second round, with valid n calculated for each questionnaire item. Frequency distributions for all items of the survey as well as cross-tabulations, where applicable, are displayed in tabular format in the Annex to this document.

5.2.1 Demographic Data

In a questionnaire section labeled “demographic data”, the participants were asked to share information on their professional affiliation, their professional background and their place of residence.

In the first round of the survey, the respondents chose from a list of six professional affiliations and an option labeled “other”, which was linked to a full-text field. Here, the participants were asked to specify their professional affiliation if it was not included in the list. Prior to launching the survey, data that were publicly available had been used to reckon the professional affiliation of the potential participants; these estimates are included as a third column in Table 5-2 below. We had estimated that the majority of the experts whom we attempted to contact were affiliated with academia; this group indeed represented the majority in both rounds of the survey (cf. Table 5-2 below). Between the first and the second round of the survey, the percentage of entries in the field “other” decreased from 11.6% to 3.8%; a category “public private partnership” was added for the second round to reflect full-text entries in the first round.

Table 5-2 Professional affiliation of survey participants

Professional affiliation of survey participants (n)				
		Round one*	**Round two***	***Experts attempted to contact****
Academia		53.6% (60)	54.7%(29)	*48.2% (187)*
Non-governmental organization		14.3% (16)	11.3% (6)	*13.9% (54)*
Other		11.6% (13)	3.8% (2)	*8.3% (32)*
Industry		10.7% (12)	11.3% (6)	*8.5% (33)*
National government / parliament		5.4% (6)	7.5% (4)	*17.5% (68)*
International organization		4.5% (5)	7.5% (4)	*3.6% (14)*
Public Private Partnership		n / a	3.8% (2)	
	Total valid	100% (112))	100% (53)	*100% (388)*
Missing	-77	25.8% (41)	27.3% (21)	
	0	3.8% (6)	3.9% (3)	
	Total	29.6% (47)	31.2% (24)	
Total		100% (159)	100% (77)	

* Self-reported during the survey / **Professional affiliation assumed prior to the survey on the basis of available data

The second item in this section, labeled ‘professional background’, also offered six categories in the first round, which increased to eight in the second round to accommodate full-text entries of the first round. (Table 5-3) For this item, multiple responses were possible. In contrast to the item labeled ‘professional affiliation’ above, where it had been possible to draw conclusions to professional affiliation from Email-addresses of potential participants prior to the first round of survey, we did not endeavor to research the professional backgrounds of the individual experts whom we contacted. Table 5-3 thus exclusively displays self-reported data of the respondents during both rounds of the survey. As shown in Table 5-3 below, the majority of the respondents had a professional background in the life sciences or in public health.

Table 5-3 Professional background of survey participants

Professional background of survey participants* (n)		
	Round one	**Round two**
Medicine	36.4% (43)	32.1% (17)
Other	33.1% (39)	8.9% (5)
Public Health	30.5% (36)	26.8% (15)
Law	8.5% (10)	10.7% (6)
Political Science	7.6% (9)	12.5% (7)
Economy	4.2% (5)	0.0% (0)
Biology / Biomedical Sciences	n / a**	30.4% (18)
Pharmaceutical Sciences	n / a**	17.9% (10)
Veterinary medicine	n / a**	1.8% (1)

*Multiple responses were possible / **n/a: these categories were added in the second round based on details given in the "other"-field during the first round

In the last item of this section (Table 5-4 below), we asked the participants to indicate their place of residence, for which three categories had been listed, i.e. developed country, developing country and threshold country / emerging market. Prior to launching the survey, we had estimated from data on professional affiliations or Email addresses that 218 of the experts whom we attempted to contact came from Europe, 36 from Africa, 21 from North America, ten from Latin America, nine from Asia, and one from the Middle East. The distribution of participants in the three relevant categories remained rather stable in both rounds of the survey (Table 5-4), with the clear majority of the experts residing in a developed country.[67]

[67] Caution may have to be exercised when drawing conclusions from these data or when using the items as a break variable in cross-tabulations. To illustrate, one participant from a developed country asked to sent in a filled-in paper version of the questionnaire by regular mail, and authorized the author to perform the online-entry of the data. The background of the request was that the participant currently resided in a developing country (and indicated this in the questionnaire) and had very limited access to the internet. We assume that, owing to the fact that the question was labeled "place of residence", the results for this item will include experts from developing countries who temporarily / currently reside in developed or threshold countries, or vice versa.

Table 5-4 Place of residence of survey participants

		Round one (n)	Round two (n)
Developed country		74,8% (83)	75,5% (40)
Developing country		18,9% (21)	20,8% (11)
Threshold country / emerging market		6,3% (7)	3,8% (2)
	Total valid	100% (111)	100% (53)
Missing	-77	41 (25.8%)	27.3% (21)
	0	7 (4.4%)	3.9% (3)
	Total	48 (30.25)	31.2% (24
Total		100% (159)	100% (77)

5.2.2 Causes for the Treatment Deficit for Neglected Diseases

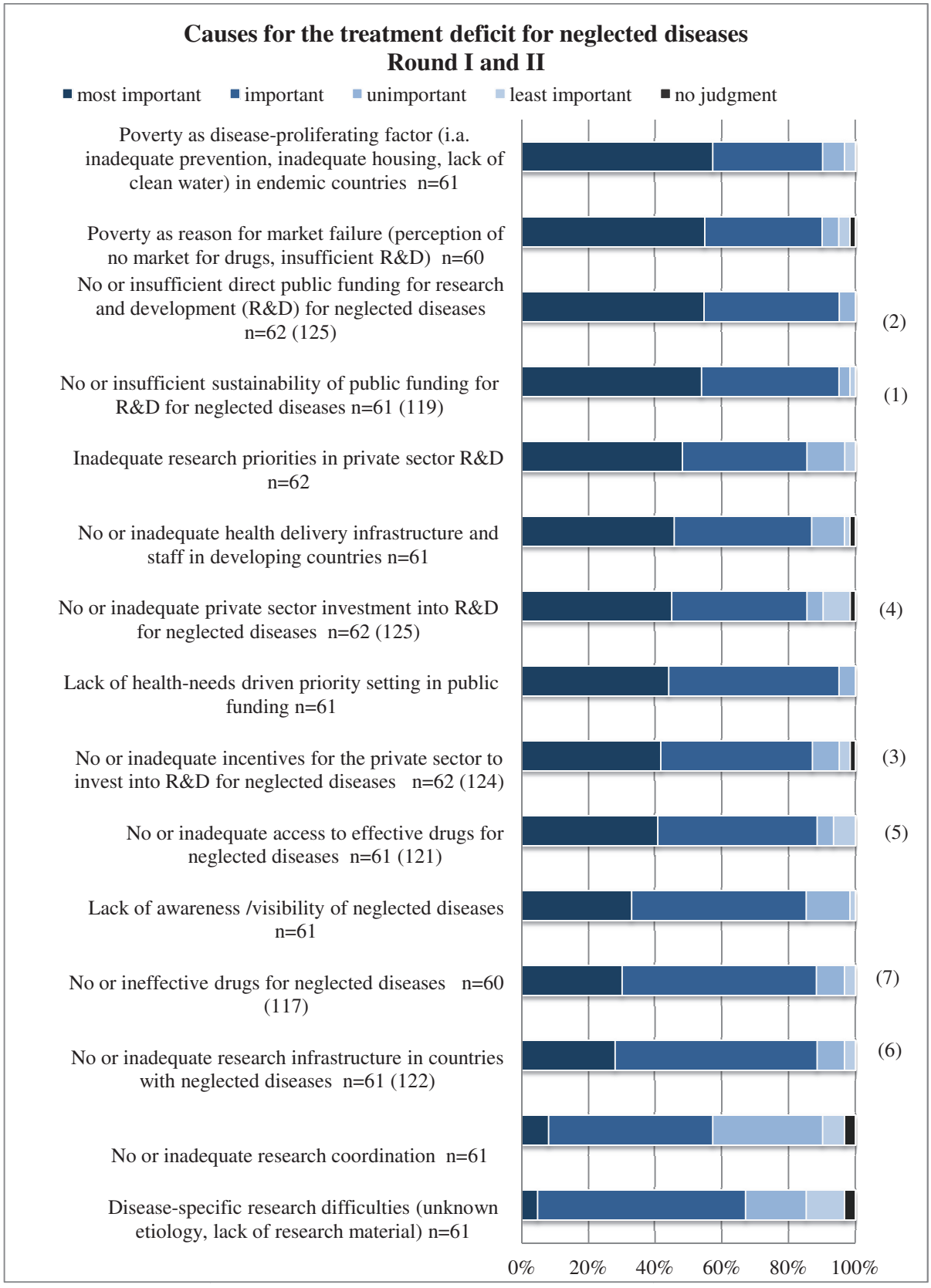
In the first chapter of the survey, we asked the respondents for an assessment of the causes of the treatment and R&D deficit for neglected diseases. Seven causes, retrieved from literature, made up the list of items in the first round, complemented by three full-text fields for each participant. During the first round of the survey, the respondents offered more than ninety suggestions for new or modified causes. Some participants underlined that the scope of this chapter would have to be broadened beyond the issue of medical R&D. The respondents' suggestions were clustered (cf. p. 76), and the list of likely causes was expanded to 15 items in the second round. The majority of the respondents' suggestions related to structural / policy deficits in developing countries (category 200), to the inadequacy of current incentives (category 300) and to a lack of awareness and advocacy (category 600). In both rounds, the causes were to be ranked according to importance.

As illustrated in Fig. 5-2 below, in the first round, the respondents identified insufficient sustainability of public R&D funding as the most important cause for the lack of treatments, yet it was by no means the only important cause. Indeed, in the first round, only one item ('no / ineffective drugs for neglected diseases') received less than 80% of aggregated positive responses (most important / important). Standard deviations ranged from 0.5 to 0.9, indicating consensus among the panelist on the majority of items in the first round. Most consensus was established on the importance of a lack of adequate direct public funding (δ 0.5) as major cause for the treatment deficit for neglected diseases. Least consensus was

established on the items “no or inadequate access to drugs” and “no or ineffective drugs for neglected diseases” (both δ 0.9).

In the second round of the survey, poverty as disease-proliferating factor received the highest ranking as the most important cause. It may be argued, however, that, strictly speaking, the item does not describe a cause for the treatment or R&D deficit, but for the persistence of neglected tropical infectious diseases. Of interest, ‘Disease-specific research difficulties (unknown etiology, lack of research material)’, an item added to the list of causes for the second round, received the lowest score in the most-important-category, but was ranked highest of all items in the adjacent ‘important’-category. When aggregating the two positive categories, 13 of the 15 causes listed were considered very important or important by more than 80% of the panelists; only two items, i.e. disease-specific research difficulties and no or inadequate research coordination received less than 80% of aggregated positive replies. Most consensus was established on the importance of a “lack of health-needs driven priority setting in public funding” and on the item “no or insufficient direct public funding for research and development (R&D) for neglected diseases” (both δ 0.6) Least consensual items were ‘no or inadequate private sector investment’ (δ 0.9).

Fig. 5-2 Causes for the treatment deficit for neglected diseases - Round I and II



**Numbers in brackets at the end of the bars show the ranking of the items in the first round.*

Cross-tabulations were performed to explore differences between subgroups in the responses for this section. The differences in group sizes in both rounds (e.g. academia n=60 / Round I and n=29 / Round II compared to international organization n=5 / Round I and n=4 / Round II) and the small size of some subgroups ruled out a direct comparison between the subgroups. Neither subgroup maintained its ranking for the most important cause between the two rounds of the survey. This may be due to changes in the group's composition between rounds, with subsequent new preferences. It may also be due to the availability of new and more differentiated items in the second round. The members of the subgroup 'academia' rated items from the initial list of causes to be most important in both rounds ('no or inadequate private sector investment into R&D for neglected diseases' / Round I and 'no or insufficient direct public funding for research and development (R&D) for neglected diseases / Round II). In contrast, the majority of the subgroup 'industry' ranked 'no or inadequate incentives for the private sector to invest into R&D for neglected diseases' as most important cause in the first round, shifting to the new item 'no or inadequate research infrastructure in countries with neglected diseases' in the second round. The subgroup 'national government / parliament' shifted its ranking from 'no or inadequate direct public funding for research and development (R&D) for neglected diseases' and 'no or inadequate private sector investment in to R&D for neglected diseases' in the first round to the new item 'inadequate research priorities in private sector R&D'. In the subgroup 'non-governmental organization', 'no or insufficient sustainability of public funding for R&D for neglected diseases' was rated most important in the first round, giving room to the new items 'inadequate research priorities in private sector R&D' and 'lack of health-needs driven priority setting in public funding' in the second round. Differences in opinion thus not only existed between, but also within subgroups, and refined wording and new items re-focused the rating of the causes in the second round. Table 5-5 below shows which causes the experts in the different subgroup ranked highest in both rounds in the category "most important".

Table 5-5 Most important causes for the treatment deficit * Professional affiliation-Round I and II

	Academia	Industry	International Organization	National government / parliament	Non-governmental organization	Other	Public-private-partnership
Round I	(n=60): no or inadequate private sector investment into R&D for neglected diseases (39%)	(n=12): no or inadequate incentives for the private sector to invest into R&D for neglected diseases (50%)	(n=5): no or insufficient sustainability of public funding for R&D for neglected diseases (60%); no or inadequate research infrastructure in countries with neglected diseases (60%)	(n=6): no or inadequate direct public funding for research and development (R&D) for neglected diseases (50%); no or inadequate private sector investment in to R&D for neglected diseases (50%)	(n=16): no or insufficient sustainability of public funding for R&D for neglected diseases (46.7%))	(n=13): no or inadequate direct public funding for research and development / R&D for neglected diseases (46.2%) (subgroup existed only in Round I)	
Round II	(n=29): no or insufficient direct public funding for research and development (R&D) for neglected diseases (67.9%)	(n=6): no or inadequate health delivery infrastructure and staff in developing countries (83.3%)	(n=4): *no majority for either item in the list*	(n=4): inadequate research priorities in private sector R&D (100%)	(n=6): inadequate research priorities in private sector R&D (66.7%), lack of health-needs driven priority setting in public funding (66.7%)		(n=2): no or inadequate private sector investment into R&D for neglected diseases (100%) (subgroup was created for Round two)

** The table displays only those causes which received the highest ranking for "most important" in the subgroups .Valid n are given for each round of the survey. The percentages in brackets refer to the number of participants in the respective group who ranked this item as most important.*

In the first round, cross-tabulations of the section on causes for the treatment deficit by place of residence showed no notable difference to the total results for the category “most important”. Respondents from developing, developed as well as threshold countries considered the lack of public funding and insufficient sustainability of public funding to be most important for the treatment deficit for neglected diseases. In the second round, the majority of respondents from developed countries (n=22 / 29) rated the lack of public funding, the lack of sustainability of public funding (n=21 / 29) and poverty as disease-proliferating factor (n=20 / 29) to be most important. In the subgroup of the respondents from developing countries, a majority chose the inadequacy of private sector investment (n=8 / 11) as most important cause; another seven items were considered most important by n=7 / 11 respondents from developing countries. There were only two respondents in the subgroup “threshold country / emerging market”; their priorities in the category “most important” were evenly spread their over the different items in the list.

The questionnaire for the first round offered full-text fields primarily to add items to the list of causes, or to modify them. At the request of the respondents, full-text comment fields were added to the section on ‘Causes’ in the second round. The comments which were received in the second round are displayed in Text box 5-1 below. Comments referred to methodological aspects as well as to the content of the section. To illustrate, one respondent pointed to the need for further differentiation in the question on the lack of health delivery, infrastructure and staff in developing countries. Another respondent perceived the scale as being imprecise, and commented on overlaps in the list of items.

Text box 5-1 Comments on the questionnaire item relating to causes for the treatment deficit / Round II

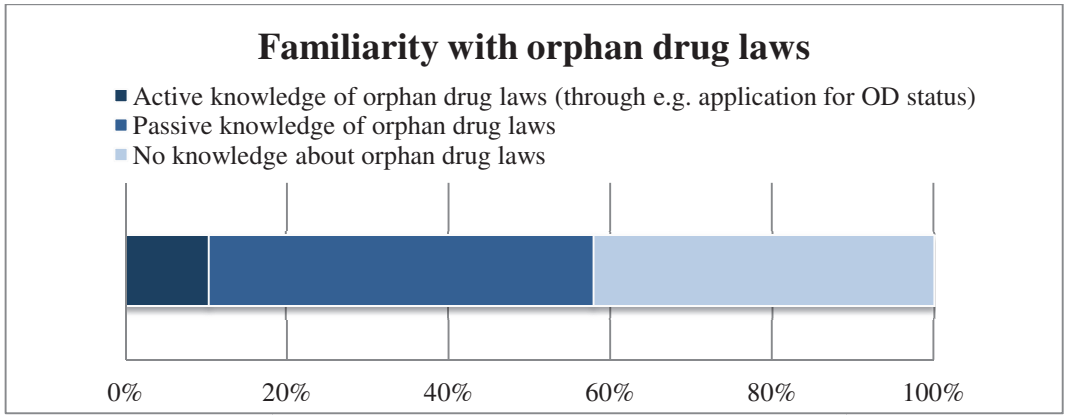
- Major issue is the lack of funding for research. Scientists wanting to work on diseases prevalent in developing countries generally do not get funding for research even from the Governments of the country where the diseases may be prevalent.
- probably a lot of efficient drugs exist ....in the cardboards in private sector R&D
- questions 2,7 and 8 are essentially the same, the key question being number 7, Like it or not the private sector is the driver of bio-medical R&D and is commercially driven. Therefore appropriate incentives are vital.
- Difficult to answer this question, since for each disease different aspects are more or less prominent
- Although there are many contributing factors, the most important is perhaps the lack of FINANCIAL incentives for private sector expenditure on commercialising leads, where they exist, in a system that is based almost exclusively on patents as the motive force.
- The area will never be of interest to Farma. Therefore funding must be from official or Foundation sources
- Treatments, out of patent most often, exist for treatment of MND, but delivery and trained teams are questionable
- Re: An effective health delivery staff and infrastructure in countries with neglected diseases does not mean one that is similar to a developed country infrastructure and staff. So its lack may signal a lack of resources and investment for health systems, but it may also signal than the globally available health "solutions" are inadapted to the specific situation in the countries with neglected diseases. It is a difficult decision to put priority on one (adapting the health delivery infrastructure) or the other (creating solutions that are more adapted to the existing situation)
- Q15 : the question on poverty as a cause for market failure could be complemented with one on inequality. Emerging countries where a significant middle class develops become "solvable markets" for drugs or medical technology: this may actually make the situation of the still dominant poor part of the population worse.
- not sure what you can deduce from this listing - most listed items are clearly important (and there's much overlap), so what are we going to learn from "important" versus "very important"?

5.2.3 Orphan Drug Regulations for Rare Diseases

Since orphan drug regulations have long been discussed in the scientific community as a possible blue print for incentives to stimulate R&D into neglected diseases, it was of interest to learn whether the panelists were familiar with orphan drug acts, and how they rated the acts' provisions for their original purpose, i.e. to promote drug development for rare diseases. The first of the three questions in the section on orphan drug acts for rare diseases, entitled "Are you familiar with orphan drug laws?", served as a filter question and offered three answering options (active

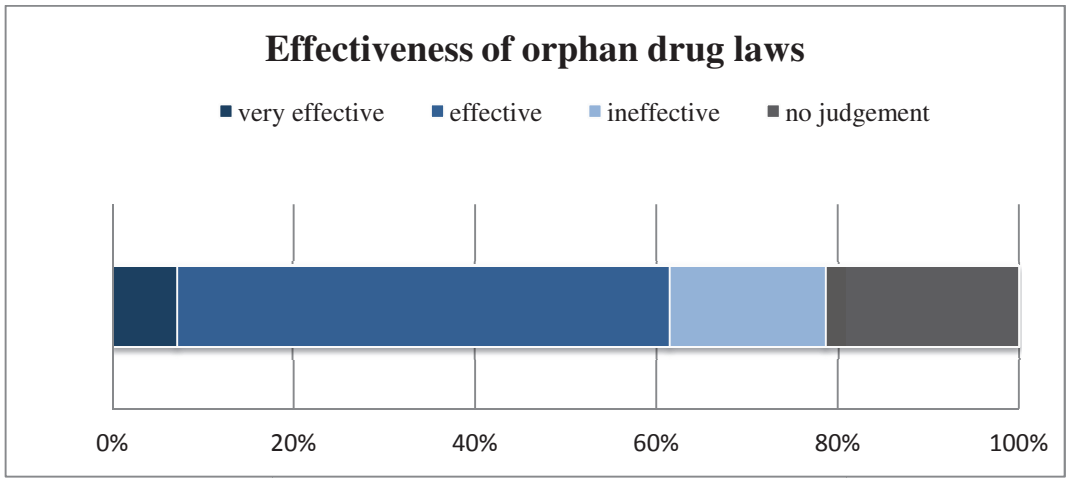
knowledge, passive knowledge, no knowledge). Respondents who answered "no knowledge" skipped the following two questions on the effectiveness of orphan drug laws and their incentives. N=126 panelists responded to this question, of whom 42.1% (n=53) reported to have no knowledge about orphan drug laws. (Fig. 5-3)

Fig. 5-3 Familiarity with Orphan Drug Laws



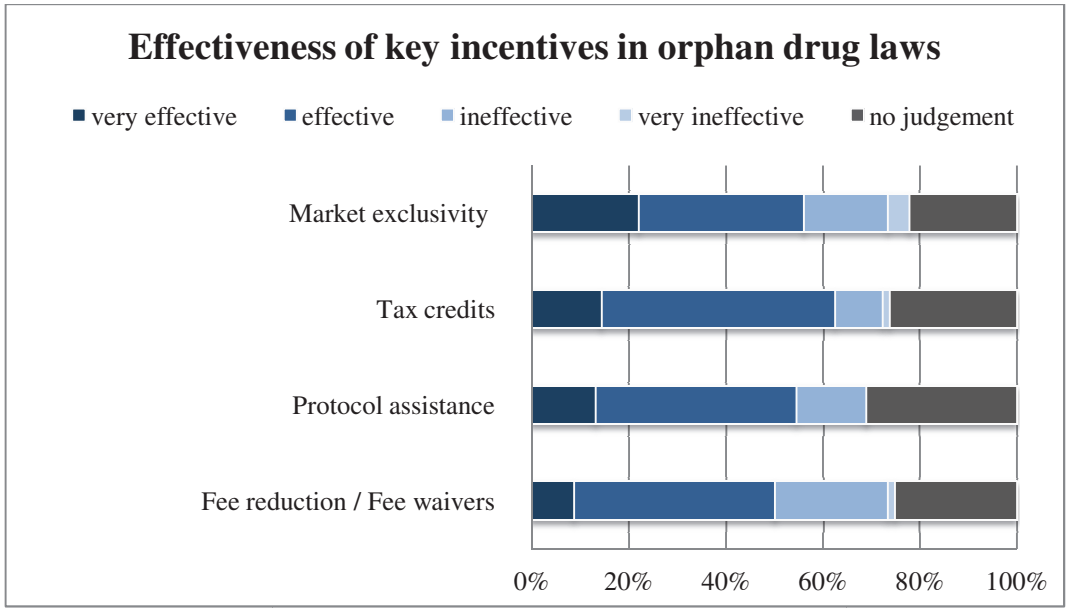
Of the remaining respondents (N=73), 10.3% (n=13) reported active knowledge of orphan drug laws (i.e. active involvement in the application for orphan drug status), while 47.6% (n=60) indicated passive knowledge (e.g. through publications). These two groups proceeded to the questions on the effectiveness of orphan drug acts and of their provisions for rare diseases. As shown in Fig. 5-4 below, more than half of the experts who responded to the question considered orphan drug laws very effective or effective; 17.1% said the laws were ineffective, no respondent chose the option "very ineffective".

Fig. 5-4 Effectiveness of orphan drug laws for rare diseases



Of the four key incentives of orphan drug laws, i.e. market exclusivity, tax credits, protocol assistance and fee reduction / fee waivers, which the experts were asked to rate, market exclusivity was given the highest score in the category "very effective", followed by tax credits, protocol assistance and fee reduction or fee waivers. (Fig. 5-5)

Fig. 5-5 Effectiveness of key incentives in orphan drug laws



Subtotals of the positive scores for the incentives (very effective / effective) revealed that tax credits were given the most approval (62.3%, n=43), followed by market exclusivity (55.9%, n=38), protocol assistance (54.4%, n=37) and fee reduction / fee waivers (50.0%, n=34). The quota for "no judgment"-replies in the section on the laws' effectiveness, and on the effectiveness of their provisions, was between 20-30%, which may be owing to the number of respondents (47.6%) who replied that they had passive knowledge of orphan drug laws.

The results from the first round were displayed in the feedback during the second round of the survey, and the respondents were given the opportunity to comment on the results in a full-text field. Comments are displayed in Text box 5-2 below. As shown by the first comment, it seemed that it had not been entirely clear to all participants that the section dealt with the performance of orphan drug laws for *rare* diseases, and not with their applicability to neglected diseases. This should have been made clearer in the design of the questionnaire. The comments expressed critical as well as favorable opinions on the concept of orphan drug acts and their

incentives. Two comments dealt with an obvious lack of visibility of orphan drug laws, which was also reflected by the 42.1% of respondents who replied that they were not familiar with these laws.

Text box 5-2 Comments relating to the results of the questionnaire item on orphan drug regulations for rare diseases

- as said before: effective to what goal? to get more neglected diseases R&D underway, or new products available to the patients (I do not know of any concrete example - maybe that would be a more interesting question)? Or to get more products / projects with orphan drug status? for example: Market exclusivity only works when there's a market. so how can it be effective for diseases which do not represent a market?
- Drug laws are not well vulgarised in the scientist / researcher communities.
- I believe the outcome accurately reflects reality.
- the laws seem to be generally effective if not well known
- Because there is little or no appropriate funding (ideally competitive grant funding from taxpayers) the laws don't matter because the research will not be done regardless of what the laws are.
- The effectiveness of various incentive schemes depends on whether or not they involve push or pull mechanisms. Pull mechanisms involving the private sector will only work if there is a successful outcome, i.e., the company is successful in developing and marketing a drug. I would be more in favour of push mechanisms.
- Canada is the only developed country in the world not to have an Orphan Drug Policy
- Curious that 43% of persons said they had "no" knowledge of orphan drug legislation, and consistently about half that percentage professed to having "no judgment" about the value of such laws. I suppose the other half who 'knew nothing about orphan drug laws' had no issues with offering opinions about its effectiveness.[68]
- looks OK
- I think participants are battling to give a simple answer to a complex question, about which most have "passive" knowledge. That explains the relative dominance of the "yes, OK" type responses.
- Belonging to the 43% who know nothing of the laws I have not answered
- The high level of lack of active knowledge of laws is quite interesting. This shows that these laws although they may exist, do not seem to be very effective or do not brought to the knowledge of the public in an effective way (e.g. through the health systems).

[68] This comment refers to the frequency distributions in the feedback included in the second round of the survey. A note was included in the feedback that only those participants who had answered ‚yes' to the question on knowledge about orphan drug laws (either active or passive) were led to the subsequent questions on the laws' effectiveness. The conclusion drawn here is thus not correct, but it informs the author that the explanations should have been given in more detail.

Text box 5-2 continued

- These outcomes show how the ideology of patents and market exclusivity persists in the area of orphan diseases, which has lead to the exorbitant prices of orphan drugs for relatively rich patients. Whereas market exclusivity can lead to an abuse of the orphan drug legislations -- as it has already been the case -- it would seem appropriate to consider that incentive mechanisms for neglected diseases will have to be tailored according to a different logic. Drugs for neglected diseases should, quite clearly, be developed as public goods. In fact, this should be a patent free territory to develop if we really want to promote availability, affordability and access to people in need.
- I agree with the effectiveness of these tools, but some of them are not relevant for neglected diseases ; anyway, the major factor behind orphan drugs success in rich countries is their outstanding price, totally irrelevant for neglected diseases.

5.2.4 Measures to Promote R&D into Neglected Diseases

In both rounds of the survey, measures to promote R&D into neglected diseases were to be ranked for desirability and feasibility. Sixteen measures, gathered from literature search and from document analyses, had been formulated for the first questionnaire. The participants had been asked in the first round to add to, or modify, the list of measures, and they contributed 134 suggestions. Based on these suggestions (cf. 4.4.3, p. 72), the list was expanded to 50 measures in the second round. Complete frequency distributions for these measures are shown in the Annex to this document (Table 8-10, Table 8-11, Table 8-12, Table 8-13). In line with our research question, this chapter will focus on the results for those items which are contained in orphan drug regulations and in the draft Medical Research and Development Treaty. The chapter also includes the ranking of all 16 items of the first round, as well as those items of the list of 50 which more than 50% of the respondents considered most desirable in the second round.

5.2.4.1 Orphan drug incentives for neglected diseases

In both rounds of the survey, tax credits, protocol assistance and fee reductions / fee waivers were viewed positively both concerning their desirability and as well as their feasibility. (Fig. 5-6, Fig. 5-7, Fig. 5-8, Fig. 5-9) One participant contrasted tax-based funding for R&D and tax credits, stating that *"it has to go through taxes and public funding; tax reduction to companies can never be a 'lasting' commitment, the research program will be cut as soon as the company realizes that it is lost money."* Market exclusivity received the lowest scores for desirability as

well as for feasibility. Still, over 20% of the respondents considered in desirable and about 40% considered it a feasible measure to promote R&D into neglected diseases.

Fig. 5-6 Desirability of orphan drug incentives for neglected diseases- Round I

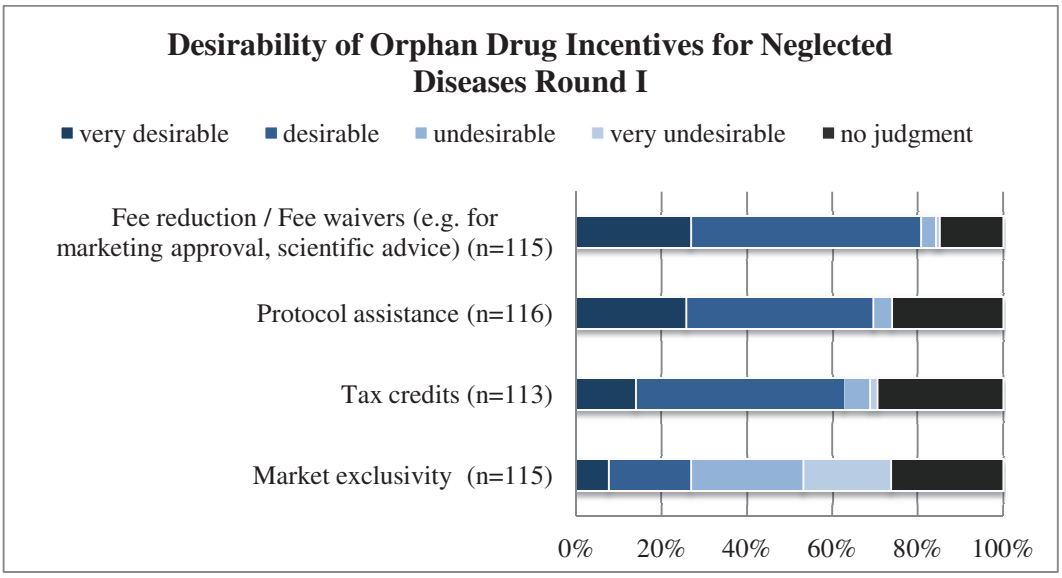


Fig. 5-7 Desirability of orphan drug incentives for neglected diseases- Round II

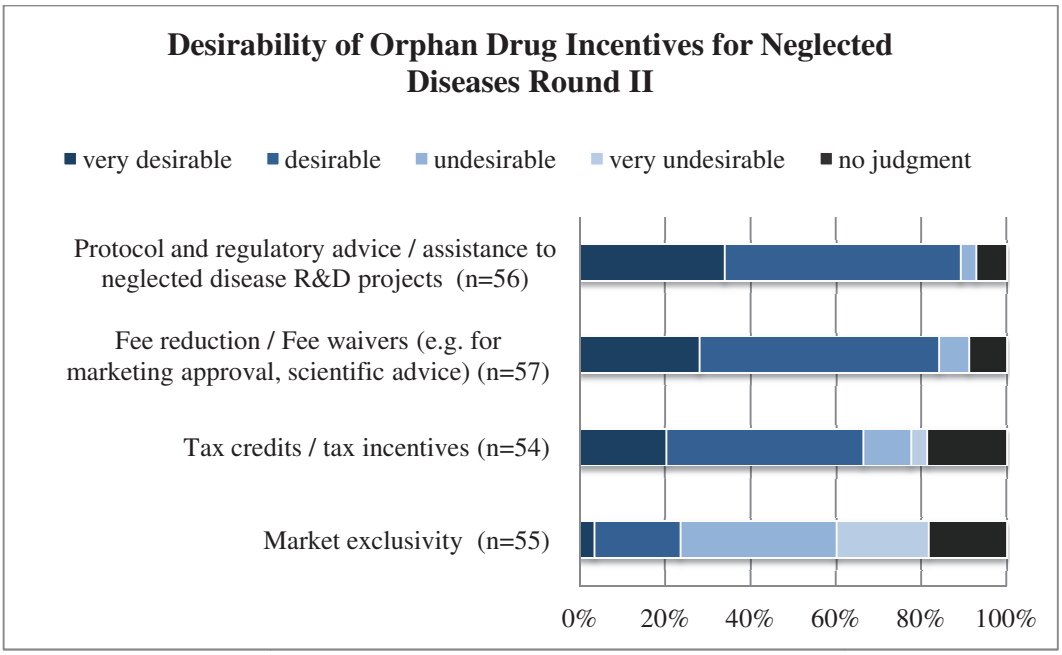


Fig. 5-8 Feasibility of orphan drug incentives for neglected diseases- Round I

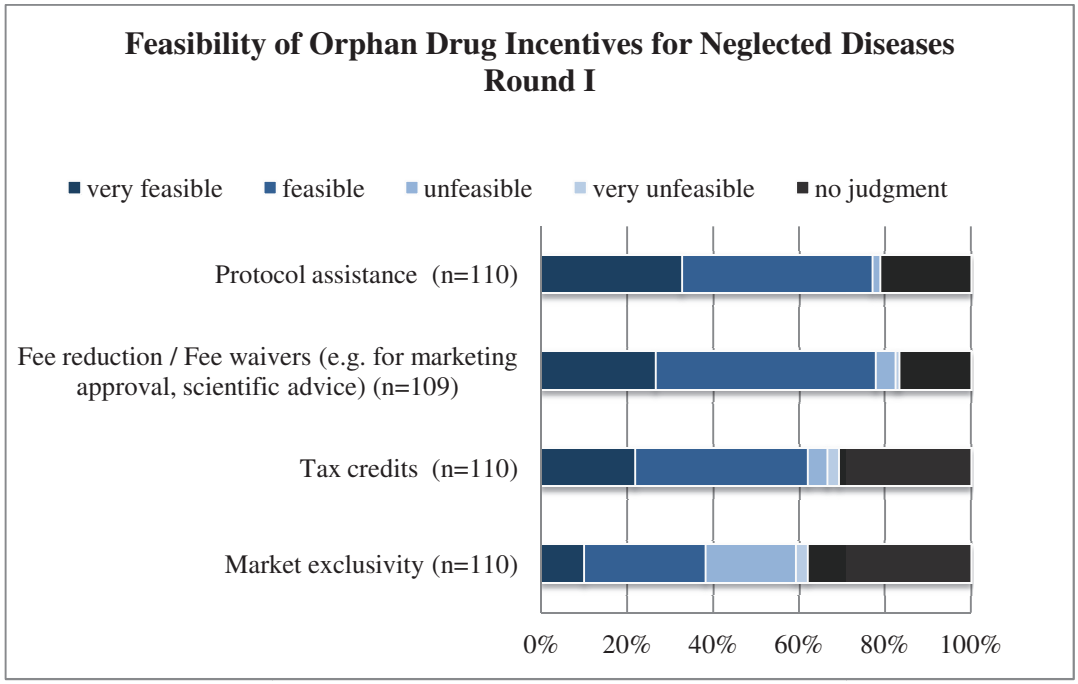
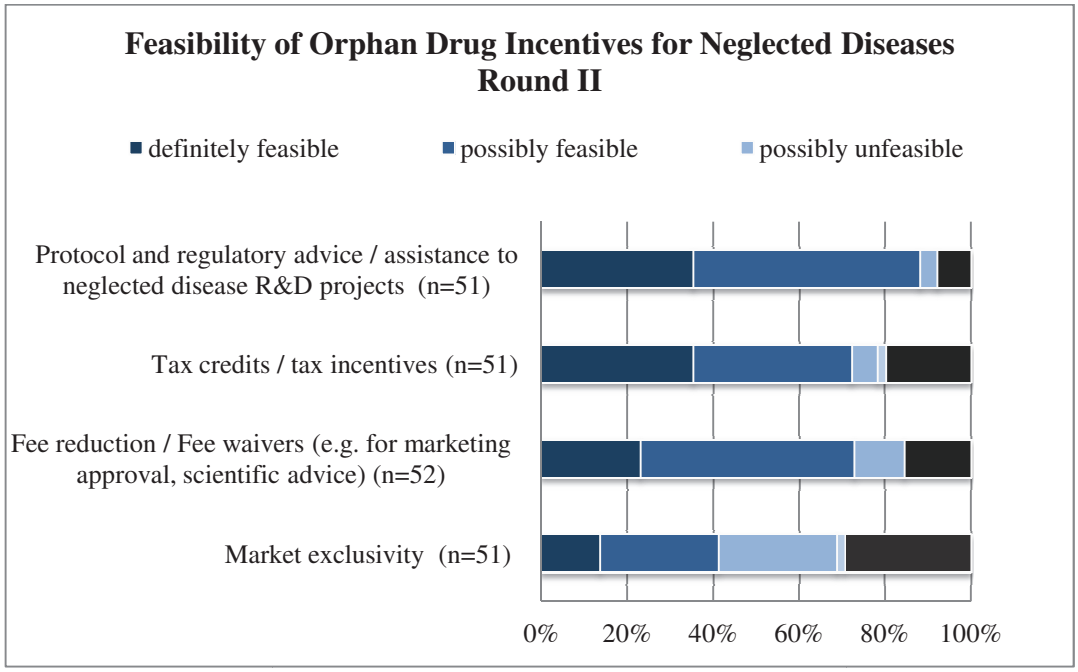


Fig. 5-9 Feasibility of orphan drug incentives for neglected diseases- Round II



5.2.4.2 Proposals of the Medical Research and Development Treaty

To ensure sustainable funding flows, the draft Medical Research and Development Treaty proposes national funding obligations for medical R&D. Prize funds based on health impact shall encourage needs-based R&D priority setting, and the separation of innovation incentives from drug prices aims to guarantee access to affordable treatments. In both rounds of the survey, the majority of the participants supported all three concepts. (Fig. 5-10, Fig. 5-11 below)

Fig. 5-10 Desirability of MRDT proposals -Round I

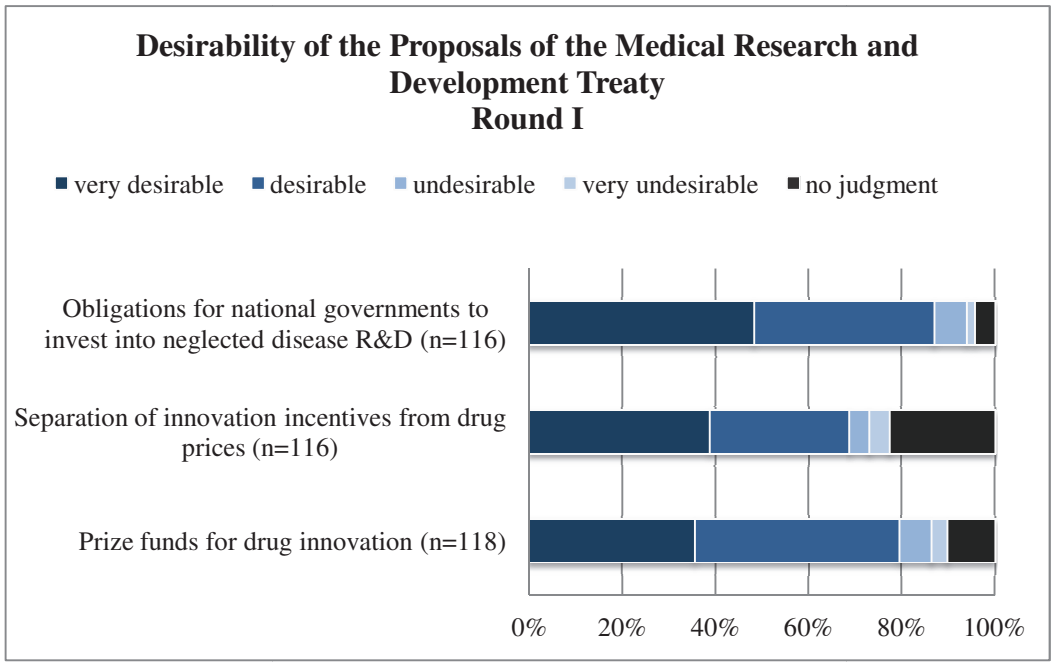
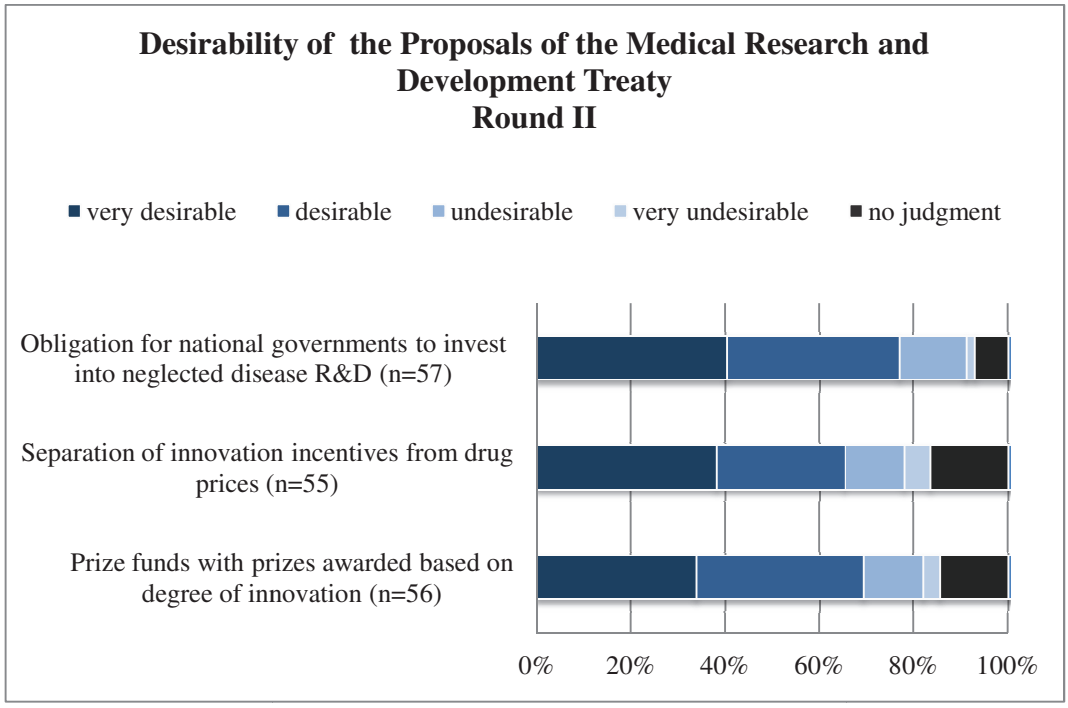


Fig. 5-11 Desirability of MRDT proposals –Round II



As for the feasibility of the three concepts (Fig. 5-12, Fig. 5-13 below), most respondents were confident that they could be implemented. The highest ranking in the category "unfeasible" in both rounds was given to the proposal to introduce obligations for national governments to invest into neglected disease R&D. About one third of the participants in the first round, and one fifth in the second round, refrained from judging the option to separate innovation incentives from drug prices.

Fig. 5-12 Feasibility of MRDT proposals –Round I

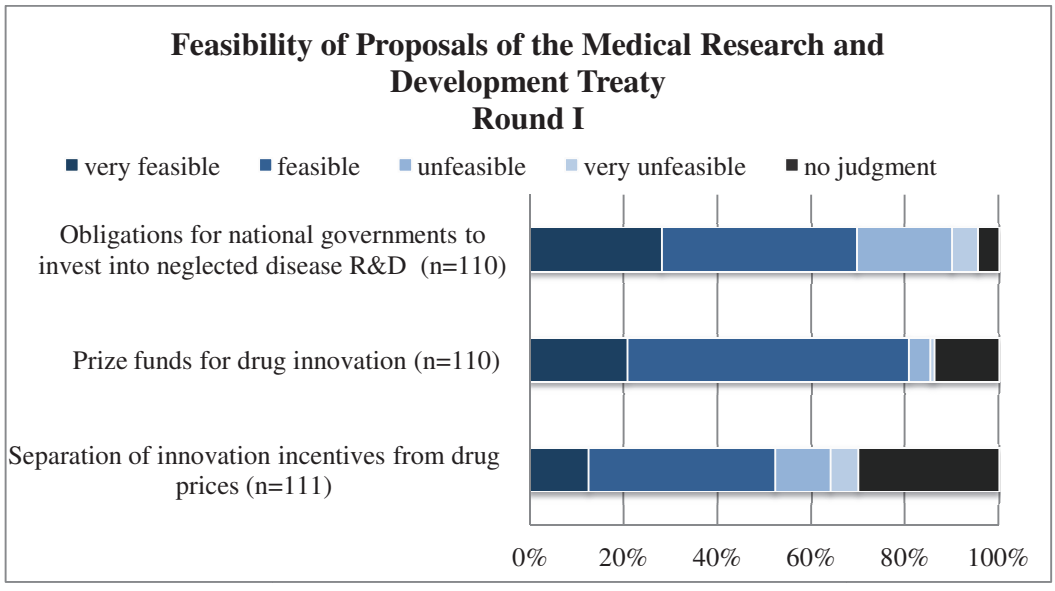
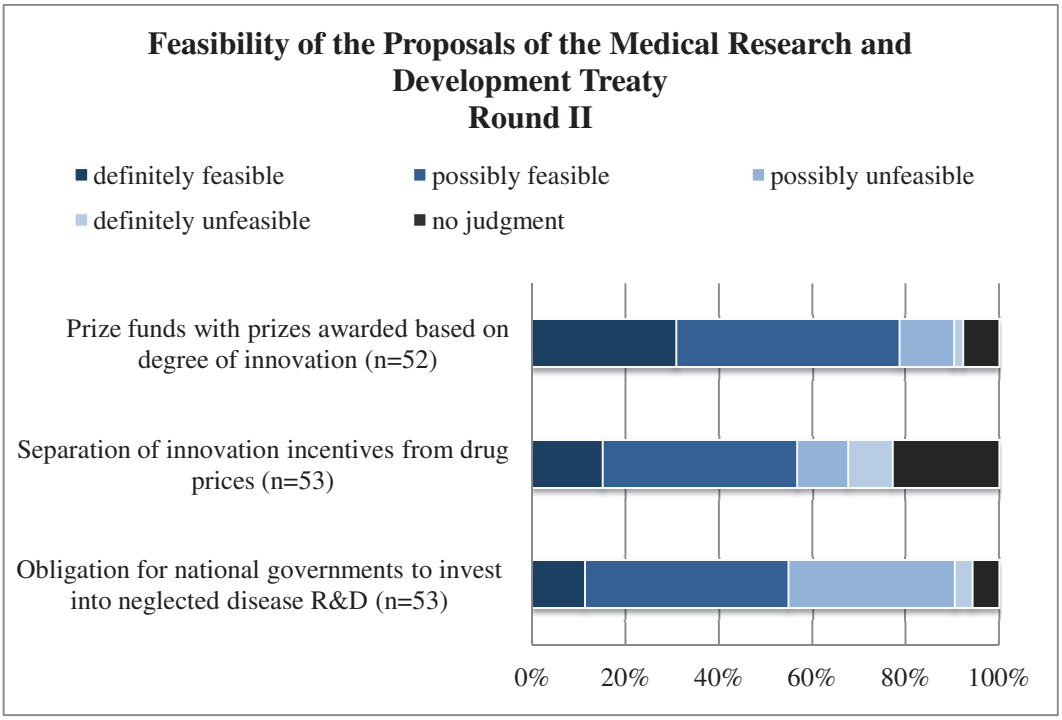


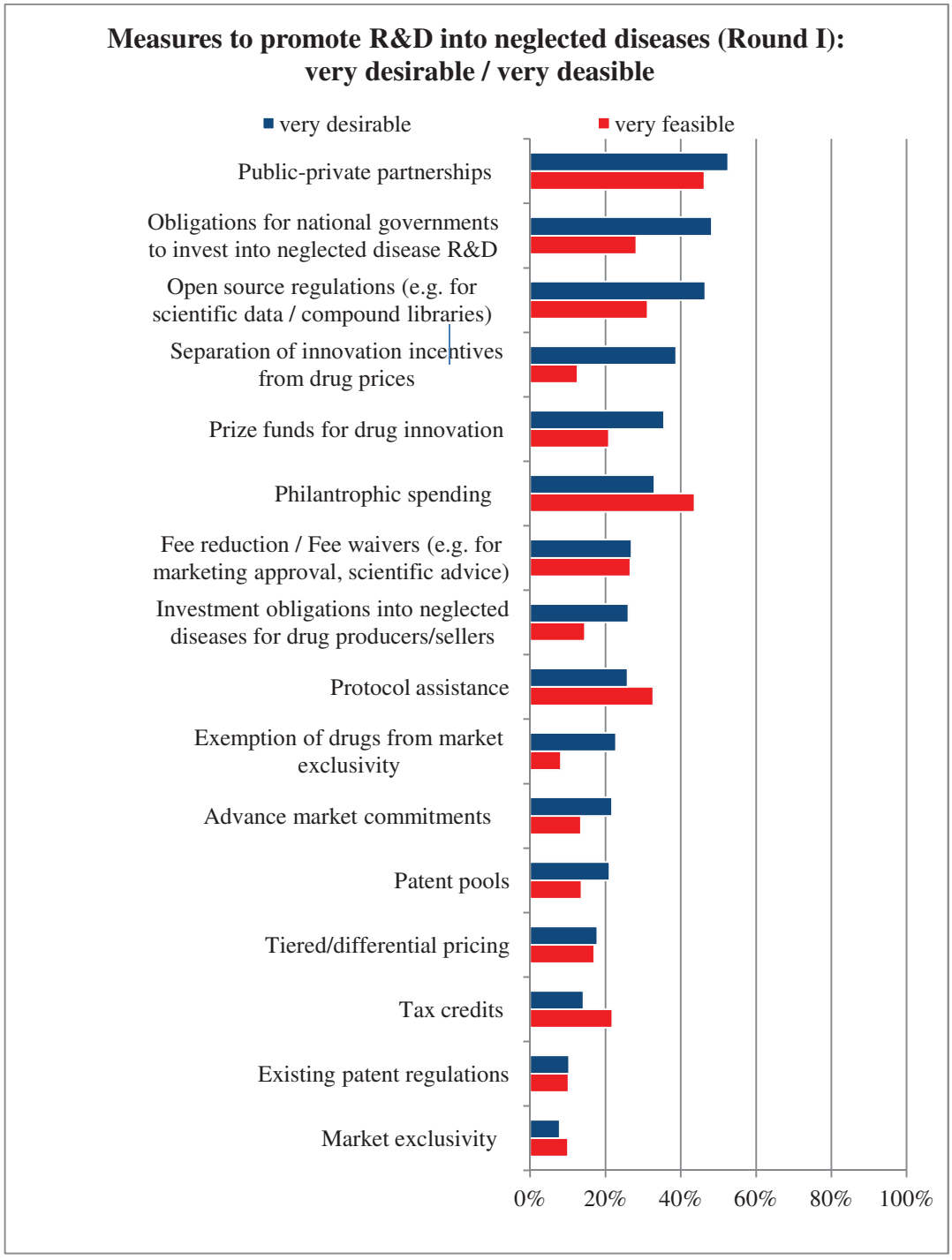
Fig. 5-13 Feasibility of MRDT proposals – Round II



5.2.4.3 Desirability and Feasibility of measures to promote R&D into neglected diseases (Round I)

Orphan drug incentives and concepts proposed in the MRDT formed part of a larger list of potential measures to promote R&D into neglected diseases in our survey. In the first round (Fig. 5-14 below), public-private partnerships were the single most desirable measure to promote R&D for neglected diseases (52.6%, n=61), closely followed by obligations for national governments to invest into neglected disease R&D (48.6%, n=56), open source regulations (46.6%, n=54), the separation of innovation incentives from drug prices (38.8%, n=45) and prize funds (35.6%, n=42).

Fig. 5-14 Desirability and feasibility of measures to promote R&D into neglected diseases-Round I



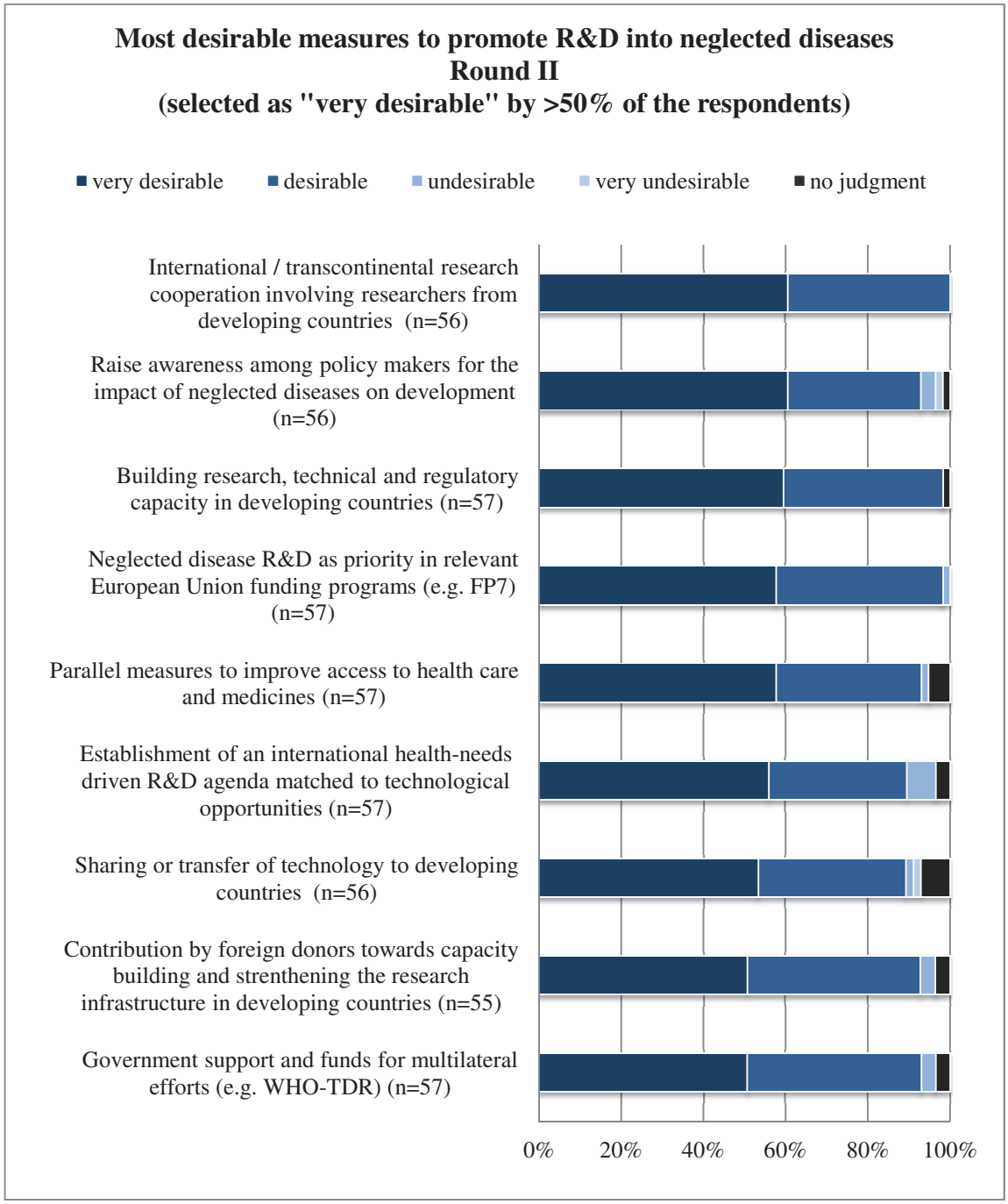
As illustrated in Fig. 5-14 above, public-private partnerships (PPPs) were also considered the most feasible measure to promote R&D into neglected diseases. Three of the 16 measures listed above showed a variance exceeding 15% between the categories "very desirable" and "very feasible", i.e. they were considered more desirable than feasible: The difference was 26.6% for the separation of innovation incentives from drug prices, 20.1% for investment obligations for national governments and 15.4% for open source regulations. Of interest, four of the sixteen

items (market exclusivity, philanthropic spending, protocol assistance and tax credits) were ranked higher in the category "very feasible" than in the category "very desirable".

5.2.4.4 Desirability and Feasibility of measures to promote R&D into neglected diseases (Round II)

In the second round of the survey, the list of measures comprised 50 items. Fig. 5-15 below shows those measures that were rated "very desirable" by more than 50% of the participants in the second round. As the three most desirable measures, the respondents selected 'International / transcontinental research cooperation involving researchers from developing countries' (60.7%, n=34), 'raising awareness among policy makers for the impact of neglected diseases on development' (60.7%, n=34) and 'building research, technical and regulatory capacity in developing countries' (59.6%, n=34).

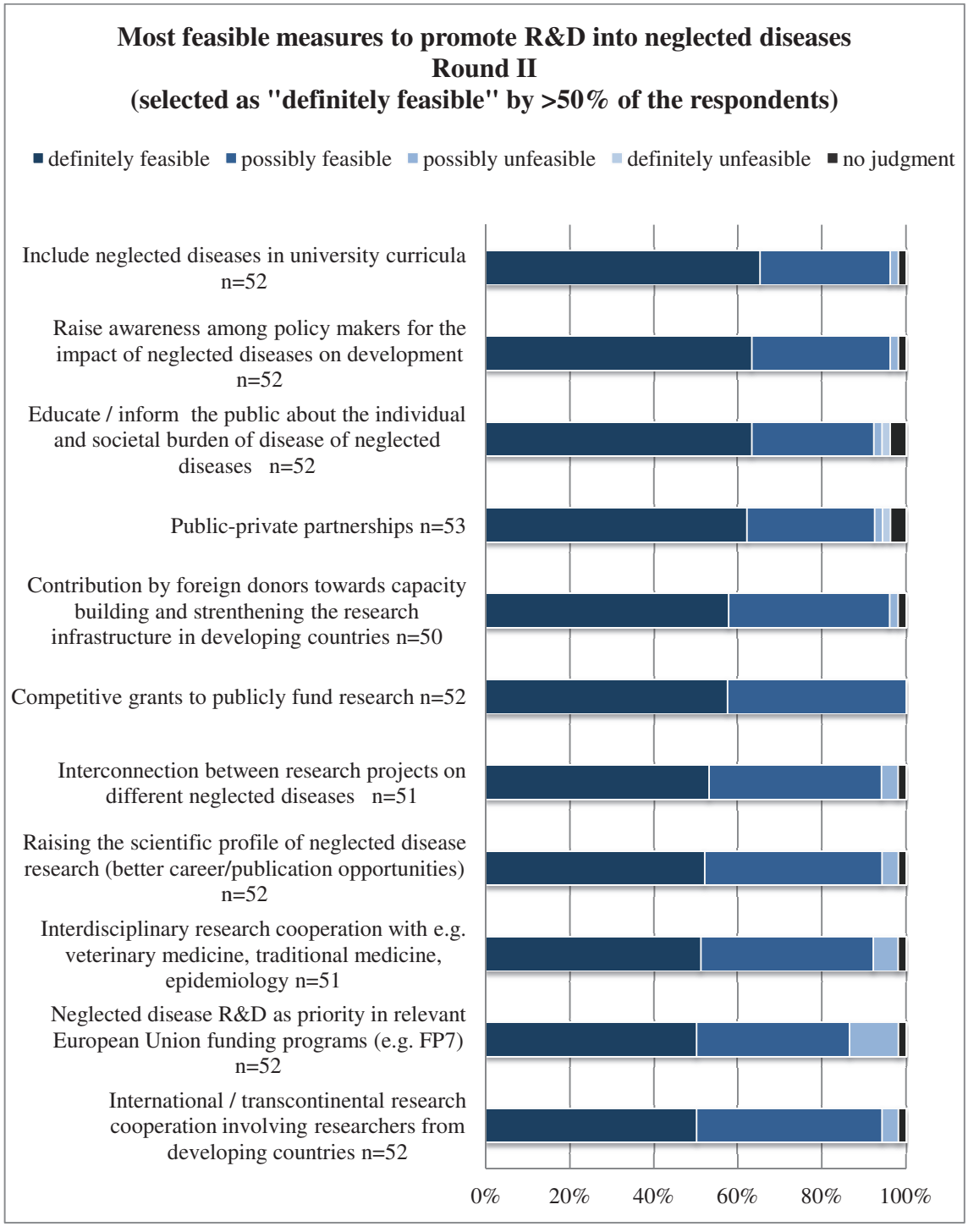
Fig. 5-15 Most desirable measures to promote R&D into neglected diseases-Round II



Least support in the category "very desirable" (s. Table 8-12 in the Annex to this document) was given to the proposal to 'introduce price increases (10-20%) for brand name drugs paid by public health programs to invest this profit in neglected diseases' (3.6%, n=2) and, secondly, to the incentive of 'market exclusivity' (3.6%, n=2). As the three most feasible measures to promote R&D for neglected diseases (Fig. 5-16), the respondents selected the 'inclusion of neglected diseases in university curricula' (65,4%, n=34), the 'education / information of the public about the individual and societal burden of neglected diseases' (63,5%, n=33) and 'raising

awareness among policy makers for the impact of neglected diseases on development' (63,5%, n=33).

Fig. 5-16 Most feasible measures to promote R&D into neglected diseases-Round II



Least feasible (s. Table 8-13 in the Annex to this document) were the suggestions to 'abolish patents' (36.5%), to establish 'price increases for brand-name drug for the benefit of neglected diseases' (19.6%) and to 'oblige the private sector to invest a given percentage of its profit in neglected disease' R&D' (17.0%)

The respondents contributed numerous comments to this section in the second round,[69] which are reproduced in Text box 5-3 below; the comments included explanations for individual votes as well as feedback on the selection of items. Several participants underlined that explanatory notes would have been helpful for some items on the list, others called for a more differentiated view or pointed out, that many of the items listed need to be seen in conjunction.

Text box 5-3 Comments on questionnaire items relating to measures to promote R&D into neglected diseases (Round II)

- unclear if you mean promoting medical R&D in general, or medical R&D for neglected diseases. I filled it in with the latter in mind, but answers cannot be generised to all biomedical R&D. For instance on patents, it would probably by harmful today to abolish all medical R&D patents (the whole biomedical R&D model being built on it), however as patents have little incentivising effect for ND the issues is very different here. Also, some proposals are unclear (cfr no judgment)
- 14) Existing regulations are very imperfect, but their flexibilities are all we've got
- Funding for research and delivery of the innovation should be made available. Developed nations should be made to realize that research and control of neglected diseases is a priority in which they have to participate.
- The question is unfair to the option of abolishing patents (which I advocate) because that option is necessary but not sufficient to foster research. People who don't understand that abolishing patents is a good idea need to be told what the replacement is before they can understand that abolishing patents is a necessary part of a package that is desirable.
- I have made no judgement on some options simply because I don't understand them. I could not answer option 18 because I advocate incentives for-profit and non-profit (including university) research (via competitive grants instead of patents) but am strongly opposed to advance market commitments (which are associated with keeping the patent system).
- What is common to both points above is that I think more explanation of the options (some of which only make sense in combination) is needed before this question could produce meaningful results.
- Some of the options presented, e.g., on IPR, cannot be evaluated as good or bad in isolation but need to be seen as part of a larger package of methods to improve the provision of medicines for orphan diseases.
- many of these are politically naive but not necessarily 'undesirable'.
- This space is still developing, post the WHO IGWG process, and so the "very desirable" list may be somewhat vague, but promising.

[69] In the first round of the survey, the chapter on measures to promote R&D into neglected diseases did not contain a comment field, only three full-text fields to amend or complement the list of measures.

Text box 5-3 continued

- Scientists like myself do not fully understand how legal, regulatory and incentive measures will affect drug availability in developing countries. The aim has to be availability of treatment for populations that are too poor to pay for it, paid for by public or private sources wherever these can be called on by national or international regulations, resolutions or incentives.
- Refocusing patents as intellectual monopoly privileges is very important
- Treaty on safety and cost-effectiveness of new health technologies linked to a competitive tender system is also very important
- Q1. I assumed it meant abolishing patents on molecules or gene sequences NOT on production processes.
- Q2. Difficult to answer: could be very useful in a patent-free context and with sufficient emphasis on "simple" biotech.
- Q36. Very desirable, but applicability limited to cases where the upfront evaluation of health value of innovation is reliably possible.
- I am not an economist and cannot answer to several questions, which I therefore marked with no judgement
- Overall this is an over-simplistic way of looking at complex issues and will only have value if followed up with a qualitative analysis. Answers to a lot of these questions would vary depending upon the governance of the proposal, the degree of compulsion to participate etc etc. It would also have been helpful to have a category that we could indicate that we didn't think the proposal would make any difference at all. did not understand Q2 or 24 or 35 or 41
- Q14. Unclear question.
- Q25. How is the true question.

5.2.5 A Regulatory Instrument to Promote R&D into Neglected Diseases

At the core of the research project was the question whether the panelists considered it desirable and feasible to have a regulatory instrument to promote R&D into neglected diseases. In both rounds of the survey, the respondents found the option (very) desirable (Fig. 5-17 below). A majority of the participants also rated it feasible, but, as illustrated by the comparatively lower number of votes for the option “very (definitely) feasible”, they exercised more caution in their votes (Fig. 5-18 below).

Fig. 5-17 Desirability of a Regulatory Instrument – Round I and II

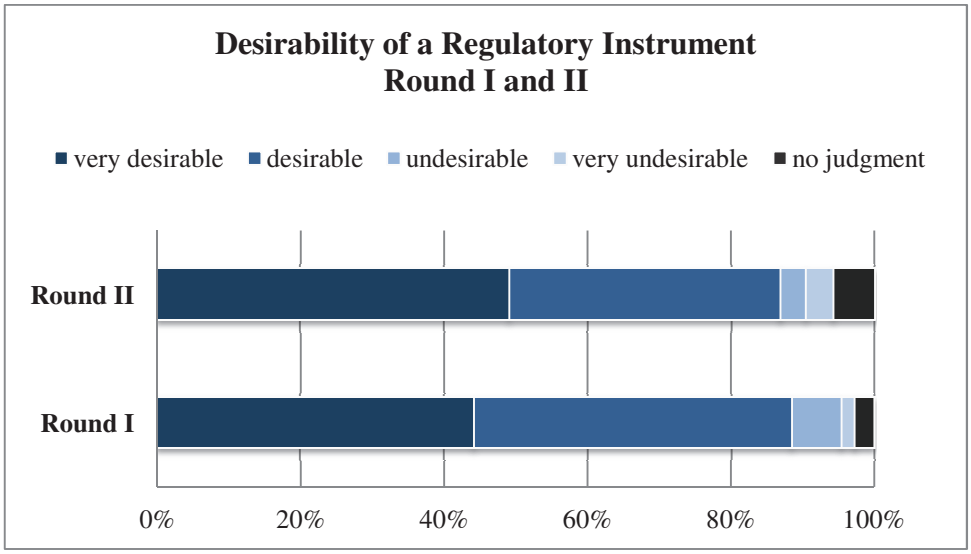
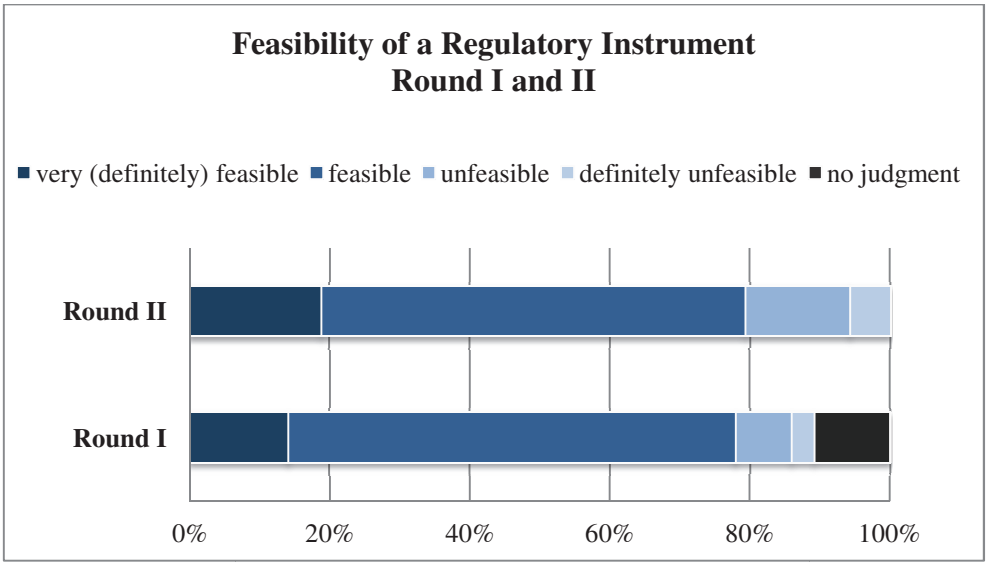


Fig. 5-18 Feasibility of a Regulatory Instrument – Round I and II



Cross-tabulations by professional affiliation were performed to explore variations in the assessment of a regulatory instrument between subgroups. (s. Table 8-26, Table 8-28, Table 8-27, Table 8-29 in the Annex to this document) Aggregated positive replies (very desirable / desirable) showed that, in the first round of the survey, five out of six subgroups were supportive of the concept of a regulatory instrument (90% / academia, 100% / national government / parliament, 100% / international organizations, 93.8% / non-governmental organizations and 100% / the subgroup "other") Of the experts affiliated with industry, 58.3% expressed a positive opinion on a regulatory instrument, while 41.6% said it was undesirable or very undesirable. In the second round of survey, experts with affiliations in academia, national government / parliament, non-governmental

organization and other affiliations again gave over 90% of support for a regulatory instrument. Opinions in the subgroup "industry" remained diverse (66.7% for and 33.3% against a regulatory instrument). Also, representatives of international organizations were less agreed in the second round; one representative considered it desirable, one undesirable and two expressed no judgment. Similarly, the two experts in the newly established subgroup 'public private partnership' were disagreed on the subject.

The feasibility of a regulatory instrument was judged positively in both rounds of survey by experts from academia (80% / 85.7%), national governments / parliaments (83.3% / 100%) and from NGOs (87.6% / 83.3%) Respondents affiliated with an international organization considered a regulatory instrument to be a feasible option in the first round; in the second round, however, three out of four experts said it was possibly unfeasible. Experts affiliated with industry were equally skeptical regarding the implementation of such instrument (50% / 66.7%).

Cross-tabulations by place of residence showed that in both rounds of the survey, the respondents who considered a regulatory instrument undesirable or very undesirable came from developed countries, which formed the largest group of respondents. The feasibility of a regulatory instrument, however, was also doubted by respondents from developing countries and from threshold countries / emerging markets (only Round II). (s. Table 8-22, Table 8-23, Table 8-24, Table 8-25 in the Annex to this document)

Nearly 60 comments were offered during both rounds of the survey on the desirability and on the feasibility of a regulatory instrument to promote R&D into neglected diseases. Supportive comments stressed that such instrument would promote sustainable funding flows for essential health R&D, encourage philanthropic spending and the formation of PPPs, increase collaboration, lay down funding obligations for developing and developed countries according to their means, and increase the visibility of NDs. Opinions differed whether regulations should be implemented at national or international level. (cf. Text box 5-4 below)

Text box 5-4 Comments from both survey rounds expressing support for a regulatory instrument

- Regulatory instruments will make more people to collaborate in the project
- I believe that a regulation should not only relate to neglected diseases, in fact if there were to be a regulation it should clearly make a reference to essential health research and development, in other words to needs-driven research, across the three typologies categorized in the CIPIH report. Immense needs for developing countries do exist in the area of type 1 and type 2 diseases as well. The idea that we should only concentrate on non-market pathologies can be very misleading indeed!
- A Treaty of some description. Political commitment will be essential.
- I believe it necessary to create some binding norms to make the public investment in essential health R&D sustainable and more democratic than it is today
- A Treaty will make possible a sustainable commitment for essential R&D with obligations and incentive for every country according to it means
- The UN should ennack a universal treaty bringing NIDs to the fore. UN should make it mandatory for ountries to invest in NID reseaexh and prvide funds for that purpos.inrease funding for the training of young sientists from the developing ountries. North south transfer of technology
- It must be an instrument aiming at both development and developing countries commitment equally and proportional to the economical capacity of each.
- Not much to say other than the failure to date to get sufficient investment in this area suggests that regulation is necessary
- if there no regulatory instrument not much attention will be given to these diseases which continue to affect most rural populations
- This is a purely national decision unlikely to be easily introduced into legislative bodies, but definitely worth trying. Once a few countries install some such instrument others will follow.
- would best be done under the auspices of the WHO
- would cover all aspects from discovery to delivery, with followup monitoring
- Only a legal instrument will extract a tacit commitment / obligation from governments.
- It is very unlikely that any change would occur in this field, if there is no concrete ruling / regulation demand a change in the R&D paradigm.
- I think it is the only approach that is likely to work, and millions of people's health is at stake.
- A collective position from governments such as in a treaty might encourage imput from phylantropic organizations, the development of public-private partnerships and might facilitate decisions such as open sourcing or limitation of fees for developed drugs in the field of neglected diseases especially through the visibility it would give the topic
- It is not possible to developp a program without a regulatory instrument.
- without regulatory instrument private R&D industry will not move
- It is a public responsability to ensure that all people can benefit for the advances in science, technology and the health sciences, and to correct possible distortions of the "free market", such as in the case of neglected diseases. The best tool available for that is to set an international regulation, or treaty. The critical issue will be its enforcability, and who will bear the cost.

Text box 5-4 continued

- Such an instrument could encourage R&D, federating financial supports from public and private parts. An additional structure will authorize a best attention towards the neglected diseases, like the new journal PLoS NTD did. More we are speaking about ND, and less they will be (neglected).

Some respondents were supportive, yet skeptical, as illustrated by the comments in Text box 5-5 below.

Text box 5-5 Comments from both survey rounds expressing skepticism regarding a regulatory instrument

- Similar to limitations and exceptions to copyright: not a perfect solution, but a necessary one. Does not look possible until it looks unavoidable. Generated bureaucracy a real problem, but not a specific one.
- Regulatory instruments are only going to be useful if there is political will to implement them and the necessary resources. Without these a regulatory instrument is a hollow statement. So far, despite nice sounding words from developed countries there has not been a great deal of commitment.
- Support the R&D treaty but would lik eto see either a separate or incorporate treaty on cost-effectivness assessment of new health technologies linked to a tender system
- Desirable if the instrument is made up of "carrot" not sticks
- In principle, it would be desireable to have consensus and / or the rule of law or regulation foster R&D but see below
- Although regulatory instruments cannot be considered sufficient to stimulate necessary R&D, there is evidence from the paediatric requrements in US law that these can promote necessary research
- very desirable but very difficult to implement without a real commitment of the states and the WHO
- Regulatory instruments are effective when appropriate to R&D of neglected diseases, however it is difficult to implement a treaty or legislate in this area
- Market forces are not working therefore some form of government intervention is likely warranted.
- If the emergence of the 'rare' in poor nations is not seen as markets to be captured, and neglected diseases for which not always new drugs but a new perspective in required are made the focus then, a treaty is meaningful for the majority of the worlds people. Issues of access, poverty, national policy priorities are issues that treaties on R&D do not address and hence will play a subsidiary role unless their context changes.
- As in my opinion this is mostly a matter of policy, a law should only define a framework (for instance on funding targets and mechanisms such as minimum contributions in proportion of GDP, on balance of incentives) and not too detailed provisions.

Bureaucracy, overregulation and a narrow focus on R&D were the tenor of those respondents, who expressed disapproval of the idea of a regulatory instrument (Text box 5-6 below)

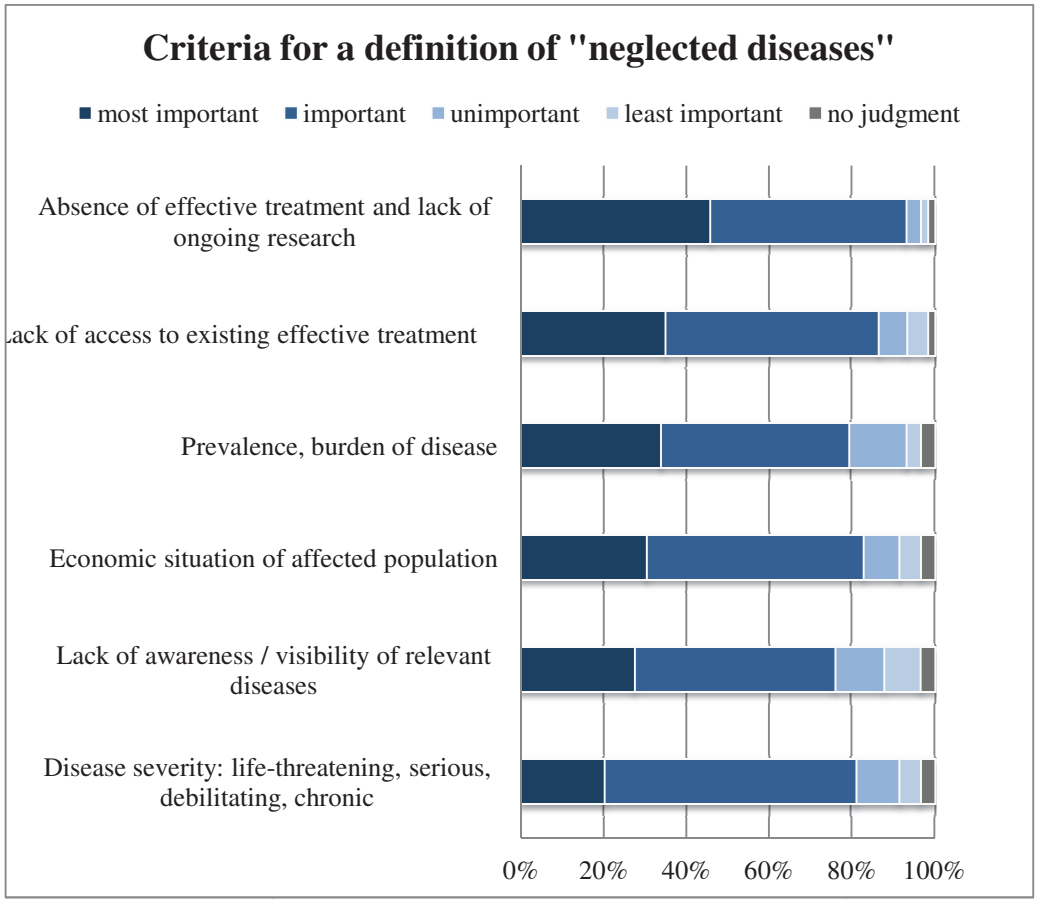
Text box 5-6 Comments from both survey rounds expressing disapproval for a regulatory instrument

- This approach is very unlikely to succeed politically and so time spent on it will be wasted. The landscape of R&D into neglected diseases has been transformed in recent years by the PPPs. We need to build on that success and model and not try and reinvent the wheel
- I don't see how this can really gurantee more useful R&D and it may cause more bureaucracy for the R&D that is already going on
- This concept overly focuses on R&D over access to existing (and new) products. The political feasibility of such an approach is minimal, and runs counter to the proven methods of incentivising R&D. We need to build on what we know works, such as PPPs and incentives, rather than risking throwing the baby out with the bathwater
- We have too much regulation already and implementation on a global basis is simply not practicable
- It is not a problem of law because in this way a law is ineffective
- Within the EU there are too many rules and regulations and funding has been very fragmented within different programmes; in neglected diseases there is the EU problem concerning migration and blood banks that needs to be attended. Laws and regulations do not replace a good educational and training system taking into account sustainability of staff and labs.

5.2.6 Criteria for a Definition of Neglected Diseases

In view of the debate to apply orphan drug regulations to neglected diseases, or to implement a medical R&D Treaty, we requested the panelists in the first round of the survey to list three criteria each that they deemed essential for a definition of neglected diseases. In total, we received 235 suggestions; owing to their homogeneity, we were able to cluster them into six key items which the respondents ranked according to importance in the second round of the survey. As illustrated in Fig. 5-19 below, close to or more than 80% of the respondents agreed on the importance for all six measures listed, whereby the degree of importance (most important / important) varied. Thus, more than 40% of the respondents considered the absence of treatments most important for the definition of neglected diseases; in contrast, only about 20% would consider disease severity to be most important.

Fig. 5-19 Criteria for a definition of “neglected diseases”



5.2.7 Participants Comments on the Method and on the Survey

To conclude, in both rounds of the survey, the respondents were asked to offer any comments they may have on the survey or on the method we applied. Several participants offered positive and encouraging feedback on our project (Text box 5-7 below), others criticized our approach. Text box 5-8 below) Thus, some respondents perceived the approach as being too superficial and simplistic; based on this assessment, they doubted the validity of the results and urged caution in their interpretation.

Text box 5-7 Participants' comments expressing support for the method

- The results will interesting and helpful for policy development
- I think it is a good idea to collect this kind of information in order to develop may be a strategy as to how more attention can be drawn towards ND's.
- Well done and clear to follow
- IT IS USEFUL IF IT IS TO BE FOLLOWED BY ACTION
- Very interesting and useful. I guess sometimes one would like more nuanced options for a more appropriate answer
- Its a very important initiation that must be followed by other institutions in order reflect and solve the problem.
- Comprehensive
- The results of this survey should be made available to governments and the private sector to help create some awareness.

Text box 5-8 Participants' comments critical of the survey design

- Some proposed options are not directly related to neglected diseases. Ranking as to importance ignores interplay among listed factors.
- Even though the scale was based on a 1 to 5, it would have been convenient to include a middle ground, which in most of the cases was not available.
- Boxes for open answers only allowed a limited number of characters limiting the ability to provide explanation for the answers given
- The survey questions are a bit blunt in relation to the current discussions at WHO. It does not reflect the reality that it is likley to require a mix of interventions to solve this problem
- I am not sure the methodology may help to solve the problem; not sure breakthrough ideas win in polls... The terms of this survey are not very intuitive. It is also questionable whether policy should be made based on the results of a survey.
- My key point relates to the simplistic quantitative nature of the survey as previously mentioned. If not followed up by a more qualitative approach I would question the value in the findings
- It does take into consideration the current debate, yet sometimes it draws too neat lines about different options, which makes answering a rather complex exercise, and potentially an ambiguous one

6 Discussion

6.1 Methodological Approach

"The Policy Delphi also rests on the premise that the decision maker is not interested in having a group generate his decision; but rather, have an informed group present all the options and supporting evidence for his consideration." (Turoff, 2002, p. 80)

The aim of this research project was to solicit stakeholders' opinions on the desirability and the feasibility of a regulatory instrument and of measures to promote R&D into neglected diseases. We chose the Delphi method to collect our data, complemented by the Text-Sorting Technique for the qualitative analysis between survey rounds, for the reasons outlined below.

A broad range of stakeholders is engaged in the debate about the R&D deficit into neglected diseases. Plentiful publications discuss the different perspectives surrounding the R&D deficit and its elimination. Expert conferences and public (web-based) hearings take place, which ensure a continuous flow and exchange of information among relevant parties. Conference documentation and proceedings, also available online, inform the interested reader comprehensively and in detail of the state of discussion, and of the different stances of the stakeholders involved. In view of these activities, we concluded that an opinion survey would not yield additional benefit to the research question at this stage. Since the project was not funded, the options for focus groups or face-to-face meetings were very limited. Telephone interviews, telephone conferences with a small number of stakeholders, or requests for written statements could have been another approach. From the available methods, we chose the Delphi method for four reasons: Firstly, the R&D deficit for neglected diseases is a global and a systemic issue. We considered a Policy Delphi to be the appropriate tool, since it is the stated aim of this method to cover as broad a spectrum of perspectives as possible for a matter under consideration. To this end, it aims to engage a survey panel of stakeholders who share a level of expertise, yet contribute various interests, professional backgrounds or affiliations. Additionally, Policy Delphi surveys can be conducted online which enabled us to contact a large number of potential participants globally. Secondly, the R&D deficit for neglected diseases is a contentious issue. It is hardly possible to

determine, retrospectively, whether the respondents would have argued differently in a non-anonymous setting. Still, we preferred to select the Delphi method as an anonymous exercise which is said to allow the participants to freely express their opinion, irrespective of any expectations and free from negative group processes. Thirdly, applying a Policy Delphi, we were able to obtain quantifiable results which allowed us to identify trends in the participants' answers. Lastly, as we had mentioned above, many fora for face-to-face debate and exchange of opinion already exist, so we were interested to explore the method's acceptance and feasibility for this area of research. From the experience gained in this project, we hoped to infer on the transferability or the extension of our methodological approach to similar, larger-scale or more in-depth follow-on projects on neglected diseases.

Of the 326 potential participants which we contacted, 159 activated the access code to the survey. Of these, 73.6% (n=117) completed the first round of the survey. In the second round, 49% of the participants (n=56 / 114) completed the survey. From the number of stakeholders who responded to the survey over a period of five months, and even more from the extent to which the participants contributed to the survey, we conclude that the method and its online implementation were practicable and well received. Positive comments which we received from the participants underscore this conclusion, while critique informed us of shortcomings in the survey design. (cf. Chapter 5, Results, Text box 5-7, Text box 5-8) From the latter, we conclude that the first round of the survey, which was based on literature review and document analysis, would have benefited from a pre-round dedicated to the development of the questionnaire items. Similar experiences were made in other Delphi surveys. (cf. Schopper et al., 2000) Some respondents criticized overlap and a lack of differentiation in some questionnaire items; others suggested explanatory notes on the concepts behind some questionnaire items. The necessity was underlined to complement the quantitative results with further qualitative data and qualitative analysis. Several participants pointed out that a list of items, such as were presented in this questionnaire, failed to acknowledge the link or interplay between, e.g., different causes for the treatment deficit for neglected diseases, or measures to promote R&D. Lastly, on the introductory page of the survey, we referred to a 'research project on neglected and orphan diseases'. Since we did not collect data on rare diseases, but only on orphan drug acts and their incentives, it

might have been more appropriate not to refer to rare diseases in the survey title; one participant communicated his surprise that the second round of the survey did not consider rare diseases or orphan drug acts for rare diseases anymore.

The Text-Sorting-Technique proved to be a valuable tool for the qualitative analysis between the first and the second round of the survey, for analyzing and clustering the participants suggestions, incorporating them into the second questionnaire, and keeping the number of items in the second round manageable. Working in a team of coders would have been helpful to increase the objectivity of the development of the category system, the newly created or modified items, and the attribution of suggestions to existing items. To illustrate, O'Loughlin et al. (2004) conducted a three-round Policy Delphi involving 52 participants, in which they used three coders for this task; if two coders assigned a contribution to the same category, it was accepted.

To conclude, the following points can be summarized as the key lessons learned for the methodological approach of this project:

- Include experts / stakeholders in the formulation of questionnaire items to ensure *i.a.* the relevance and differentiation of questionnaire items

- Include explanatory notes for questionnaire items

- Increase the research team for the qualitative analysis to enhance the objectivity of the process and its results

A Policy Delphi is a "forum for ideas" (Turoff, 2002, p. 96), aimed at complementing and supporting decision-making processes of committee debates. Its objective, as we have noted in the introduction to this thesis, is to collect, explore and correlate views from a heterogeneous panel, and to present to political decision makers a range of options on which they may base their informed decision. (Linstone & Turoff 2002). Many valuable suggestions which the respondents contributed still await further in-depth analyses. Particularly the section on measures to promote R&D into neglected diseases increased considerably between the first and the second round. A third round could have been meaningfully added solely focusing on measures which shall be included in a regulatory instrument,

perhaps distinguishing push- from pull mechanisms within such third round. Also, it could have been of interest to explore among the participants whether a potential regulation should specifically be devoted to neglected diseases, as orphan drug acts target rare diseases, or whether it is preferable to have a document which embraces all medical research and development relevant for developing countries, also for Type I diseases, as one respondent commented. Lastly, it would have been of interest to learn whether, in the long run, a biomedical R&D treaty would also embrace rare diseases.

To further benefit from the data gathered, they could serve to develop a follow-on Delphi survey, perhaps a consensus exercise, endowed with adequate financial and personnel infrastructure and resources, to take the research question from exploration to consensus-building. To this end, the issue will have to be narrowed and focused, e.g. on measures to be included in a regulatory instrument. The process of iteration will have to be based on a manageable agreed list of items, preferably developed by a team of researchers and experts in a pre-round to the actual survey. The number of rounds, and / or threshold levels for consensus, would have to be determined. To explore dissensions (Turoff, 2002) and to underline the concept of Delphi surveys as a communication device among experts (Helmer, 1977), or stakeholders, questionnaires should provide ample room for comments.

It is recommended that a Policy Delphi is followed by a working group which may utilize the results to formulate policy recommendations. (Turoff, 2002) Several respondents to the survey indeed suggested that the results be made available to decision-makers to complement, and maybe further stimulate, current debates on the issue. The results of the survey were initially presented as a poster and abstract at the 7th European Congress on Tropical Medicine (Oct.3-6,2011). (Fehr et al., 2011a). A first analysis of the survey data was published in November 2011 in BMC Health Services Research. (Fehr et al., 2011b) Based on this publication, Professor John-Arne Røttingen, who chaired the WHO Consultative Expert Working Group: Finance and Coordination, included selected outcome data of our survey in his presentation of the Final Report of the Working Group on the occasion of a public seminar ("Strengthening the Global R&D System - Innovation for

Health Needs in Developing Countries", Global Health Programme, Graduate Institute, Geneva, May 4, 2012) [70]

Taking into consideration the qualifying aspects mentioned above, we thus conclude that the method allowed us to engage a large number of stakeholders and to collect, analyze and present data which attracted interest in the public health community. The following section will discuss the results of the survey.

> *"We need to tackle the political determinants of health." (Kickbusch, 2005, p. 247)*

6.2 Results

6.2.1 A Regulatory Instrument to Promote R&D into Neglected Diseases

The research project centered on the question whether a regulatory instrument is desirable and feasible to facilitate and promote R&D into neglected diseases. From the longstanding and ongoing debates about the application of orphan drug acts to neglected diseases and the implementation of a draft Medical Research and Development Treaty, we had inferred on a sustained interest in such option. This, we could confirm with our Delphi survey. Close to 90% of the respondents gave a positive answer (very desirable / desirable) to the question of the desirability of a regulatory instrument; nearly 80% in both rounds also considered it (definitely) feasible. In their comments, the respondents expressed the hope that a regulatory instrument would ensure sustainable funding, encourage philanthropic spending, firm up obligations by developed and developing countries, increase collaboration, democratize investment in essential R&D, increase the visibility of neglected diseases, and enable the development of public private partnerships. Several participants expressed doubts as to the necessary political will for such instrument. One respondent commented: "*Regulatory instruments are only going to be useful if there is political will to implement them and the necessary resources. Without these*

[70] http://graduateinstitute.ch/globalhealth/Events_Global_Health_Programme/Seminar4May/page12766.html

a regulatory instrument is a hollow statement. So far, despite nice sounding words from developed countries there has not been a great deal of commitment." Some respondents criticized the focus of such instrument on biomedical R&D; others considered the approach of a regulatory instrument unnecessary and inappropriate, anticipating further red tape.

6.2.2 Causes for the Treatment Deficits and Measures to Promote R&D into Neglected Diseases

When conceptualizing the survey, we considered it important to ask the respondents to rank and identify likely causes for the R&D and treatment deficit so as to identify causes to which a regulatory instrument would have to respond. Most important, in the view of the respondents, were the lack of (sustainable) public funding, a lack of private sector funding, and a lack of R&D infrastructure in developing countries. Further to these, the respondents named inadequate priority-setting both in the public and in the private sector, market failure, a lack of incentives and of the visibility of neglected diseases. To respond to these deficits, national funding obligations, as well as grants and relevant priority-setting, e.g. in EU Framework Programmes, were advocated.[71] Over 90% of the respondents highlighted the importance of government support and funding for multilateral efforts, such as WHO-TDR; further proposals for investment of public funds included the establishment of public (or affordable) preclinical research facilities' and public funding to phase III clinical trials. Proposals to increase private sector funding included incentives as well as obligations for the private sector. More than 60% of the survey participants advocated investment obligations by the private sector for the benefit of neglected diseases; the assessment of the feasibility of the latter concept was 50% in the first round, and below 30% in the second round. Philanthropic spending has played an increasingly important role in recent years in promoting R&D into neglected diseases, and the majority of respondents considered philanthropic spending (very) desirable to promote R&D into neglected diseases. Yet while the contribution of large funders, such as the Bill and Melinda Gates

[71] At the time of this writing, the 7th European Framework Programme (2008-2013)-program includes a priority area on neglected infectious diseases, focusing on trypanosomiasis (sleeping sickness), leishmaniasis, Chagas' disease, Buruli ulcer, leprosy, trachoma, infantile diarrhea, lymphatic filariasis, schistosomiasis and soil-transmitted nematodes.
(http://ec.europa.eu/research/health/infectious-diseases/neglected-diseases/pdf/nid-leaflet_en.pdf)

Foundation, is widely acknowledged, philanthropic spending does not address what have been named inherent flaws in the systems, i.e. patents and high drug prices to recoup investment. Moreover, by the sheer volume of the Gates Foundation's involvement, it necessarily sets priorities in public health, which, as some argue, should be the responsibility of the public sector and its democratically elected bodies. (cf. Lob-Levyt & Schaaber, 2009; Hein & Kickbusch, 2010) Perhaps correspondingly, philanthropic spending was one of the items which was rated more feasible than desirable in this survey. On the other hand, based on suggestions by the survey participants, two items relating to philanthropic spending were included in the questionnaire; the first one referring to foreign donor contributions towards capacity building and strengthening research infrastructure in developing countries, the second item to private donations to 'real' pharmaceutical companies to develop drugs for neglected diseases. The first proposal was supported by over 90% of the respondents, the second suggestion was considered desirable by about 40%.

According to the respondents, measures to increase the visibility of neglected diseases would have to be directed at academia, political decision-makers and at the general public. Proposals to correct the lack of priority-setting for neglected diseases in the public as well as in the private sector included suggestions to lower private sector influence, to establish an international health-needs driven R&D agenda and to have a global funders forum to set priorities. It may be considered in this context that patient advocacy has greatly contributed to the development and implementation of orphan drug regulations. A shared feature of patients afflicted with neglected diseases, however, is their low political voice. (WHO, 2010g; Hampel, 2004) In the absence of strong and well-organized patient advocacy groups, international, non-governmental and humanitarian organizations attend to and plead the cause of patients with neglected diseases. It has been noted, however, that a growing number of actors may also pose a risk of a duplication of work, requires high coordinative efforts, and sometimes may even overstrain the recipient countries. (Hein & Kickbusch, 2010; Moran et al., 2009c)

A lack of research infrastructure in developing countries was identified as a key cause for the R&D deficit for neglected diseases. Consequently, several proposals were made to the effect of building research infrastructure as well as research capacity in developing countries. Of the ten most desirable measures selected in the

second round of the survey, three referred to international cooperation involving researchers from developing countries and to the building of research, technical and regulatory capacity in developing countries. In fact, international / transcontinental research cooperation involving researchers from developing countries was the most desirable of all measures to promote R&D into neglected diseases. This outcome highlights a strong interest both in building expertise in endemic countries, and in benefiting from existing expertise of researchers from developing countries. Broad support was also given to items referring to the interconnection of research projects on different neglected diseases, the establishment of interdisciplinary cooperation and innovation clusters and of links to existing infrastructures for HIV / Aids, malaria, and tuberculosis.

In addition to the above aspects of promoting R&D into neglected diseases, the respondents underlined the importance of taking measures to promote access to existing drugs.

6.2.3 Orphan Drug Acts for Rare and for Neglected Diseases

Orphan drug acts include push and pull mechanisms to promote drug development for rare diseases.[72] The acts have been hailed for their performance in stimulating the development of products for rare diseases, and criticized for enabling block-buster orphan products, double-burdening tax-payers, generating pseudo-orphan products or impeding access to orphan drugs. The ongoing debate about orphan drug acts' application to neglected diseases raised our interest in the stakeholders' assessment whether orphan drug incentives could be of benefit for neglected disease product development. As a precursor to this assessment, we had been interested to learn how many of the respondents were familiar, and to what degree, with orphan drug acts, and how they assessed the effectiveness of orphan drug incentives for rare disease R&D. It was not the aim of these questions, however, to proceed to an in-depth discussion on the performance of orphan drug acts for rare diseases; this

[72] Push mechanisms, such as grants or tax credits, encourage and assist the launching of research projects, while pull mechanisms aim to compensate a drug producer for the absence of a profitable market. Callan and Gillespie (2007) concluded that push mechanisms bear a greater risk for intransparency than pull mechanisms, since they cannot always be traced back to a specific product. Pull mechanisms, so it is argued, are considered politically attractive, since they are outcome-oriented, address a specific need, and are limited in funding and time. (Callan & Gillespie, 2007)

debate is being conducted elsewhere with detailed and comprehensive data. We found that, despite the fact that orphan drug schemes have long been debated as blueprints for mechanisms to promote R&D into neglected diseases, most recently in the WHO Consultative Working Group (WHO, 2012g), more than 40% of the N=126 participants who replied to the question in our Delphi survey, were not familiar with orphan drug laws, meaning that they had neither active nor passive knowledge of such regulations. The subsequent two questions in our survey, dealing with the regulations' performance for rare diseases, were rated by about 60% of the N=126 respondents who had indicated that they had either active or passive knowledge of orphan drug acts. The majority (61.4%) of these considered orphan drug acts very effective or effective, whereby only 7.1% selected the ranking "very effective". With 22.1%, market exclusivity was given the highest ranking in the category "very effective" of the four listed incentives; the highest aggregated positive reply (very effective / effective) was given to tax credits (62.3%). The quota for "no judgment"-replies in this section was rather high (20-30%), which may link to the number of respondents who, in the initial question about the familiarity with orphan drug laws, reported only passive knowledge (47.6%), versus 10.3% who had active knowledge (e.g. having been involved in applications for orphan drug status). In sum, we found that orphan drug acts were not very well known among the participants of our survey. It may be of interest to correlate this outcome with findings which show that orphan drug acts, even where applicable to neglected diseases R&D, are barely utilized. (cf. WHO, 2010e) We assume that the concept raises little interest in the neglected disease scientific community, owing to the fact that the debate about orphan drug acts centers on market exclusivity and its inapplicability to resource-poor settings. In fact, in both rounds of the survey, the respondents considered market exclusivity to be among the least desirable measures to promote R&D into neglected diseases. This assessment underlined once more that this incentive, which is conceptualized for financially well-equipped health systems and affluent (compared to neglected disease patients) patient populations, is not of benefit in settings where patients cannot, or barely can afford to pay for drugs out of pocket, and lack social security systems to turn to. One respondent to the survey remarked:

> "These outcomes show how the ideology of patents and market exclusivity persists in the area of orphan diseases, which has lead to the exorbitant prices of orphan drugs for relatively rich patients. Whereas market exclusivity can lead to an abuse of the orphan drug legislations -- as it has already been the case -- it would seem appropriate to consider that incentive mechanisms for neglected diseases will have to be tailored according to a different logic. Drugs for neglected diseases should, quite clearly, be developed as public goods. In fact, this should be a patent free territory to develop if we really want to promote availability, affordability and access to people in need."

Further results of the section on measures to promote R&D into neglected diseases revealed, however, that more than two thirds of the respondents in both rounds considered push incentives of orphan drug acts, i.e. tax credits, fee waivers and protocol assistance / scientific advice, desirable and feasible to foster R&D for neglected diseases. A majority of the respondents advocated selected pull mechanisms for neglected diseases. In both rounds of the survey, nearly three quarters of the respondents supported exclusive funds for neglected disease R&D, or budgetary set-asides to purchase drugs for neglected diseases. About two thirds of the participants considered it a feasible option. Advance market commitments (AMCs) and prize funds to promote R&D into neglected diseases were considered desirable as well as feasible options.[73]

From these outcomes, three scenarios could be developed with regard to applying orphan drug incentives to neglected diseases, whereby push and pull incentives would be considered separately:

- Keep the status quo
- Adopt measures to increase the visibility of orphan drug push mechanisms for neglected diseases
- Create appropriate pull-mechanisms for neglected diseases product development under orphan drug acts.

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[73] In the first round of the survey, the relevant items read: "Prize funds for drug innovation" and "Advance market commitments". The wording was modified for the second round to read: "Prize funds with prizes awarded based on degree of innovation" and "Incentives for the private sector (e.g. advance market commitments, governmental incentives)"

Under the **first scenario**, neglected diseases remain eligible for orphan drug incentives, yet no particular efforts are being taken to promote an expanded application of these incentives to neglected disease R&D projects.

Under the **second scenario**, targeted needs-assessments could be conducted among stakeholders, to learn which form of assistance is required that could be provided under orphan drug acts, which incentives provided for in orphan drug acts respond best to sponsors' and researchers' needs, and which modifications of existing push incentives are considered beneficial for R&D projects into neglected diseases. Based on the outcome of such needs-assessments, push incentives could be adapted or developed within the existing framework of orphan drug acts, and their utilization could be actively encouraged and promoted in the scientific community. To illustrate, protocol assistance under the European orphan drug regulation describes an expanded form of scientific advice to sponsors of designated orphan products, which includes information on the issue of significant benefit for rare disease products. Protocol assistance for neglected disease projects could cover special requirements such as the suitability of a product for use in developing countries. (cf. WHO, 2010e) By the same token, the majority of the respondents in the survey agreed that a lack of (sustainable) public funding was the most important cause for the R&D deficit for neglected diseases; correspondingly, they advocated relevant priority-setting in public funding programs. Grants earmarked for R&D into rare diseases are included in the U.S. orphan drug act; furthermore, in 2009 a program to fund preclinical research into rare and neglected diseases was launched by the U.S. National Institutes of Health. (NIH, 2009) The EU regulation does not include a proper grant program for rare diseases, yet sponsors of designated orphan products are eligible for EU funding allocated to rare disease research. Further research could inform of the feasibility and of possible benefits of installing or expanding grant programs for rare and neglected diseases under current orphan drug acts.

Tax credits, another push mechanism, were also rated positively by the respondents as a measure to promote R&D into neglected diseases. Under the U.S. orphan drug act, sponsors of rare disease R&D benefit from tax credits for clinical research. In the context of a proposal for legislation to create tax credits for preclinical research into neglected diseases, introduced in the U.S. House of Representatives in 2009, it

has been argued that tax credits, while not covering the total costs for R&D investment into a product for neglected diseases, would still function as an incentive, because of the private sector's additional interest in showing his global responsibility. (Anderson, 2009) In the European Union, tax exemptions or tax credits for activities relating to rare disease R&D have to be offered by member states, and are included in the Inventory of national incentives. (European Commission, 2006b) The same procedure could apply to tax credits and tax exemption for neglected diseases R&D. The recent WHO Expert Working Group had excluded tax credits from the list of eligible potential incentives to promote neglected disease R&D (WHO, 2010e); equally, the follow-on WHO-Consultative Expert Working Group considered tax breaks for companies to be of little value to promote R&D into neglected diseases. (WHO, 2012g)

The **third scenario** concerning the application of orphan drug incentives could be to include suitable pull-mechanisms for neglected diseases under orphan drug acts. Having considered the option of orphan drug schemes for neglected diseases, the WHO-CIPIH had concluded that "[a]ny proposal of this nature, therefore, also needs to address the absence of a paying market, and affordability." (WHO, 2006e, p. 86) Pull mechanisms include differential, or tiered, pricing, advance market commitments, priority review vouchers or prize funds. Differential pricing (for this and the following s. Danzon, 2007) for an identical product can be applied between countries or within countries, proceeding from the assumption that more affluent middle and upper classes also exist in developing nations. It has been argued, however, that as a stand-alone measure, differential pricing is not considered helpful for Type III neglected diseases. If this incentive were to be applied to neglected diseases, it would have to be complemented by other mechanisms, such as advance market commitments. (Danzon, 2007) Advance market commitments were primarily conceptualized for vaccine development and are a "financial commitment to subsidise the future purchase of a vaccine not yet available if an appropriate vaccine is developed and if it is demanded by the poorest developing countries." (GAVI Alliance, 2007) Advance market commitments (for this and the following, s. Light, 2009) are donor-funded. In return for donor payments, drug developers agree to make a product available at a close-to cost price for developing countries whereby the company keeps its intellectual property rights for the AMC-funded product. Since AMCs are disbursed for a developed product, and R&D costs

have to be borne in advance, this incentive targets large multinational companies which are able to raise sufficient funds for the R&D process. (Light, 2009) Weaknesses and risks that have been identified for AMCs refer both to the concept (e.g. the difficulty to set product prices in advance) and to its implementation (*i.a.* the payment of AMCs for pseudo-innovations, high prices both for developing countries and for donors). (cf. Love & Hubbard, 2007) Priority review vouchers for a defined list of tropical infectious diseases were established under the U.S. Federal Food and Drug Amendments Act of 2007. (United States Congress, 2007) Recently, Ridley et al. (2010) recommended that they also be introduced in the European Union. Priority review vouchers are awarded for the successful market application of a drug for a neglected disease. (for this and the following cf. DiMasi & Grabowski, 2007; Herrling, 2007; Ridley et al., 2006; Anderson, 2009) The voucher gives the holder access to a shortened priority review period (six months instead of 10 months for standard review) for a potentially profitable product for a non-neglected disease of his choice, thereby enabling early market entrance for the profitable drug; the additional profit from early marketing approval shall recoup the investment spent on R&D for the neglected disease product. Priority review vouchers can be traded between companies. As with AMCs, priority review voucher may be a functioning incentive for large multinational companies; the fact that R&D costs have to be pre-paid, however, excludes small and medium-sized enterprises (SMEs) with no block-buster drug in their portfolio from the benefits of such incentive. Lastly, prize funds as pull-mechanisms (for this and the following cf. Love & Hubbard, 2007), aim to separate the costs of an innovation from the price of a product; they can be disbursed as milestone prizes or large end-stage prizes. Prize funds can reward medical innovation based on health impacts, thereby intending to discourage investment in me-too products. In contrast to AMCs, prize funds are linked to an obligation to allow generic production of the prized product. In the first round of our Delphi survey, prize funds were preferred over AMCs and differential pricing. In the second round, the item 'incentives for the private sector (e.g. advance market commitments, governmental incentives)' was considered more desirable than prize funds, whereby the quota for 'no judgment' was 5.3% for the item which included AMCs, and 14.3% for prize funds. One respondent explained his/her vote on this item and clearly pointed out the need for a differentiated interpretation of the quantitative survey results: "*I have made no judgement on some*

options simply because I don't understand them. I could not answer option 18 because I advocate incentives for-profit and non-profit (including university) research (via competitive grants instead of patents) but am strongly opposed to advance market commitments (which are associated with keeping the patent system)." The item 'Voucher systems in developed markets (as with the FDA) for other products' was introduced into the list of measures in the second round; 39% of the respondents considered the option very desirable, one third answered 'no judgment'. About 45% of the respondents indicated that such vouchers were feasible. 38,5%, of the respondents answered 'no judgment'; correspondingly, several respondents commented that they were not familiar with some of the concepts introduced in the list of measures in our survey.

To conclude, from the early concepts onward which explored mechanisms to foster R&D for drugs of limited commercial value (cf. Interagency Task Force to the Secretary of Health, 1979) up until the most recent WHO deliberations on innovative financing mechanisms and neglected diseases (cf. WHO, 2012g), orphan drug acts have played a role in the debate about promoting R&D for neglected diseases. It is widely agreed that the pull-incentive of market exclusivity does not respond to the needs of neglected diseases. Furthermore, orphan drug acts do no compensate for the main causes of the R&D deficit which the participants in our survey named for neglected diseases, i.e. a lack of R&D funding, of adequate priority setting, let alone poverty in endemic countries. Neither will they promote capacity building or technology transfer, as the WHO-CEWG Final Report noted. (WHO, 2012g, p. 56) Still, the question has been asked whether some benefit can be drawn from this established infrastructure also for neglected diseases. (cf. Milne et al., 2001) Proceeding from the results of our survey, we would argue that it is worthwhile to further explore whether the existing infrastructure of orphan drug regulations can be of benefit to neglected diseases. Addressing public health needs, particularly unmet medical needs for rare and neglected diseases, is named as a strategic area in the recent EMA Roadmap to 2015. (EMA, 2010b) The question of the applicability of orphan drug infrastructures could be linked to and benefit from existing analyses of push and pull mechanisms for neglected diseases. (cf. Schaaber & Wagner-Ahlfs, 2011) As Callan et al. (2007) underlined, studies and appropriate metrics are crucial to determine a proper mix of push and pull incentives for different neglected diseases. If push incentives of orphan drug acts were to be

increasingly utilized also for neglected disease product development, budgetary allowances for orphan drug acts will have to be expanded so that an extension of such services would not be to the detriment of rare diseases. With respect to the European regulation on rare diseases, this could mean an increase in the special budgetary allowance which EMA receives from the European Commission to compensate for the financial incentives under orphan drug acts.

In the face of market failure and often inadequate health and social security systems in endemic countries, pull mechanism for neglected diseases, whether or not installed under orphan drug regulations, will have far-reaching budgetary implications. As Villa et al. (2009) noted, it may be difficult to generate public support for such measures in times of cuts in health spending. Therefore, another debate should be prioritized and accompany the above analyses, which would focus not so much on the applicability of individual orphan drug incentives. Instead, it would address the issue that, after many years of thought and deliberation, it is time to act on the realization that the motives which led to the development of orphan drug acts, equally apply to neglected diseases. Measures should now be taken to translate this knowledge into political commitment and into a suitable public health strategy for neglected diseases. Orphan drug incentives were developed under premises which are different from those that apply to neglected diseases. Consequently, not all of the incentives of orphan drug acts can be meaningfully transferred. Orphan drug acts were built on the pillars of functioning health care and health insurance systems in developed countries. These prerequisites do not exist in developing countries. Contrary to the vast number of rare diseases, each of which afflict a small number of patients, WHO labels only about 14 diseases as being 'neglected', and only four of these are considered tool-deficient, i.e. no effective treatments are available for them. However, Chagas' disease, considered tool-deficient, had an infection rate of 10 million in 2009, with 35 million people at risk in 21 Latin American countries. (WHO, 2010a) Buruli ulcer, another tool-deficient disease, is endemic in approximately 33 countries; in 2010, 4.907 new cases were reported globally, 4.846 of these in Africa (http://apps.who.int/neglected_diseases/ntddata/buruli/buruli.html, Accessed 8.6.2012) For Buruli Ulcer, these numbers may seriously under-represent the true caseload, since it is not compulsory to report Buruli ulcer, and patients often do not have access to health care. In addition to tool-deficient diseases, treatments for tool-

ready diseases such as lymphatic filariasis, the world's second largest cause of disability with about 40 million people seriously incapacitated and disfigured (WHO, 2012e), are not accessible or available in sufficient quantities to prevent the disease or treat affected patients. Orphan drug acts pronounce a clear commitment that patients with rare diseases have a right to the same quality of treatment as other patients. There can be no doubt that the millions of patients who suffer from a small number of neglected diseases are as deserving of such a long-term, sustainable commitment from political decision makers as the millions of patients diagnosed with one of the 6000 to 8000 rare diseases. The figures reflecting the burden of neglected diseases, and of their effect on social and economic development in endemic regions, support an urgent call for action.

6.2.4 The draft Medical Research and Development Treaty

The draft Medical Research and Development Treaty goes far beyond the concept of orphan drug acts, and aims to respond to issues of sustainable and predictable R&D funding, of equitable access to medicines, of cost-effective incentives, needs-based medical R&D and sharing, building and transfer of knowledge, technology and capacity. Advocates of the Treaty highlight its objectives to remove economic access barriers to medical innovation by de-linking innovation incentives from drug prices, to establish needs-based priority setting and to discourage investment in me-too R&D by linking prize-funds to health impact. Perhaps owing to the far-reaching reform which it proposes, the Treaty has been called undesirable as well as politically and technically unfeasible by some. It has been criticized for its lack of enforcement mechanisms, for the anticipated need for sophisticated infrastructure to monitor funding flows, for shifting priority setting for medical R&D from the private to the public sector[74] and for its unclear relations with existing patent regimes.

The Treaty proposes to ensure sufficient and predictable funding flows through national funding obligations for medical R&D based on GDP or per capita income of signatory states. In the first round of our survey, this proposal generated more

[74] In fact, over 60% of the survey participants advocated to lower the private sector's influence on R&D priority setting as a measure to promote R&D into neglected diseases; about 40% considered it a feasible measure.

than 80% support in the categories ‘very desirable’ and ‘desirable’; close to 70% also considered it ‘very feasible’ or ‘feasible’. In the second round of the survey, the aggregated ranking in the categories ‘very desirable’ and ‘desirable’ remained high (>70%), yet the ranking in the categories ‘very feasible’ and ‘feasible’ dropped to an aggregated 55%; the votes for the category ‘possibly unfeasible’ increased from 20% in the first round to 36% in the second round. The percentage of ‘no judgment’ answers to this question ranged between four and seven percent for desirability and feasibility in both rounds of the survey. We would conclude from these outcomes, that the majority of the respondents adopted a clear stance on the item, yet anticipated difficulties for the concept’s implementation. (The category ‘possibly unfeasible’ was defined as: ‘some indication this is unworkable / severe political resistances / difficult to communicate to the public). Whether this means that the respondents doubt that states would sign a treaty, or whether they doubt that signatory states will fulfill their funding obligations – the latter doubt perhaps being nourished by longstanding debates about meeting goals for official development aid or fulfilling national commitments under the Global Fund – would have to be clarified.

Another core concept of the MRDT, which contrasts market exclusivity of orphan drug acts, is the separation of innovation incentives from drug prices to ensure equitable access to innovation. From the percentages of ‘no judgment’-votes in both rounds (16.4% to 29.7%) we infer that several respondents felt not familiar enough with this concept to offer an opinion. As has been discussed in the method section above, definitions, explanatory notes or links to explanatory publications / websites may have been helpful for the respondents and would have decreased the number of ‘no judgment’-replies. Of those who ranked the item, however, close to 70% considered the concept ‘very desirable’ or ‘desirable’ in the first round; the number slightly dropped to 65.5% in the second round. Aggregated votes for the categories ‘definitely feasible’ and ‘possibly feasible’ remained at about 55% for this item in both rounds of the survey. To implement the de-linking of incentives from drug prices, the MRDT proposes the establishment of prize funds for innovative products based on health impact, a concept which the majority of the survey respondents supported. Aggregated positive replies regarding the desirability of this proposal dropped by ten percent (79.7% / 69.6%) between the first and the second round,

while positive ratings for the feasibility of this option stayed at 80% in both rounds. The percentages for 'no judgment' replies ranged from seven to 14 percent.

The survey did not include questions on the distributed infrastructure which the Treaty proposes, and on structures to monitor funding flows; however, more 80% the survey respondents agreed on the general desirability and the feasibility of the 'establishment of accountability systems for funds received'. The MRDT includes proposals to change patent laws or to enable exemptions from existing patent laws for the benefit of neglected diseases. Regarding the controversial issue of the configuration of the Treaty's relation to the WTO-TRIPS Agreement, the recent WHO-CEWG underlined that a treaty would not replace, but complement current patent regulations (WHO, 2012g, p. 53). Of interest, a considerable shift took place in our Delphi survey regarding the issue of patents to promote R&D into neglected diseases. In the first round of the survey, close to 50% of the respondents considered existing patent regulations (very) undesirable to promote R&D into neglected diseases; in the second round, only 30.3% expressed this opinion. With 23% of 'no judgment'-replies in both rounds, a considerable number of respondents did not wish to express an opinion on the issue of patents to promote R&D into neglected diseases.

In addition to addressing funding flows for medical research and development, the MRDT would encourage signatory states to promote capacity building and knowledge/technology transfer to endemic countries. This objective corresponds closely with the measures which the survey respondents considered most desirable to promote R&D into neglected diseases. In fact, of the 135 proposals for additional measures, 26 related to capacity building, which was the highest number of proposals for one item in the relevant category system. (s. Table 4-6, p. 78)

To conclude, the draft Medical Research and Development Treaty is a complex and a comprehensive approach to promoting not only R&D into neglected diseases. It addresses a variety of the issues identified by the survey respondents as key causes for the R&D and treatment deficit as well as desirable measures to remove such deficits. In its Final Report to the Sixty-fifth World Health Assembly (May 21-26, 2012), the WHO-CEWG considered two proposals for a biomedical research and development treaty and concluded that "the time had now come for considering a

coherent and comprehensive international framework or convention". Details of the provisions of such treaty, or convention, shall be developed in the negotiation process among WHO member states. (WHO, 2012g, p. 53) The very near future will thus show whether the concept of a biomedical R&D treaty will be implemented, and which mechanisms, both regarding funding sources as well as allocation of funds, it will contain.

6.2.5 Criteria for a Definition of Neglected Diseases

At present, no precise definition exists for neglected diseases, comparable to that of rare diseases under orphan drug acts. Even though prevalence rates had initially been set arbitrarily for rare diseases, and problems have been identified with rising prevalences and indications for designated orphan products, as well as with medically plausible subsets, the epidemiological criterion offers a guideline as to what constitutes a rare disease. Furthermore, the definition of rarity in orphan drug acts acknowledged it as a unique disease-spanning feature which caused structural R&D deficits. Prior to the enforcement of orphan drug acts, drugs for neglected and rare diseases had also been termed 'significant drugs of limited commercial value' (Interagency Task Force to the Secretary of Health, 1979). For the 6th Millennium Development Goal, the wording chosen to also refer to neglected diseases was to 'combat HIV/Aids, malaria and other diseases'. Today, in the course of the shift from vertical, disease-specific to population-based approaches to combat neglected diseases, various disease-spanning features characterize the group of neglected diseases. (cf. WHO, 2010g, p. 5)

Being aware of the complexity of the task to define the neglect of tropical infectious diseases, we were still interested to learn from the survey participants which criteria they deemed important for a definition of a neglected disease. Our interest arose, primarily, from the fact that currently the diseases which fall under this label differ within and between organizations. We further assumed that, if a regulatory instrument were to be developed to promote R&D into neglected diseases, some form of a definition and underlying criteria would have to be developed. The draft Medical Research and Development Treaty stipulates that a Committee on Priority Medical Research and Development (CPMRD) will adopt targets for priority medical research and development, which includes neglected diseases. (CPTech,

2005b) The Discussion Draft 4 of the Treaty, however, did not include a definition of neglected diseases. In line with the exploratory nature of our project, we requested the participants in the survey to name three criteria each in the first round of the survey which they deemed most important to define neglected diseases. The numerous, yet homogeneous suggestions that were contributed were condensed into the following six criteria (in descending order for the ranking in the category "most important" in the second round of the survey):

- Absence of treatment and lack of ongoing research
- Lack of access to existing treatments
- Prevalence, burden of disease
- Economic situation of affected population
- Lack of awareness / visibility of relevant diseases.
- Disease severity: life threatening, serious, debilitating, chronic

The above criteria are commonly used to describe the group of neglected diseases. As has been shown in the preceding Chapter 2, however, difficulties have been encountered in gathering data and applying appropriate tools to quantify the neglect of tropical infectious diseases. The Médecins sans Frontiers (MSF) / Drugs for Neglected Diseases (DND) working group (Depoortere & Legros, 2001) connected the geographical spread, the disease's magnitude and severity, the number of drugs under clinical development, the number of publications, of people working on a specific disease and of targeted initiatives, to identify neglect and R&D priorities. Trouiller et al. (2002) correlated the number of new chemical entities (NCEs) with the number of DALYs to illustrate the absence of needs-based R&D, while G-Finder reports gather, compare and analyze data on funding flows for Type II and Type III diseases. (Moran et al., 2009a; Moran et al., 2011; Moran et al., 2009c) These efforts serve to identify deficits and needs, and to assist potential funders to direct funds to relevant research areas.

Apart from R&D deficits, the survey participants considered access deficits to be an important criterion for neglected diseases. Access deficits arise i.a. from

infrastructural problems in endemic countries, when health facilities and staff are absent or not within reach for patients, or from economic issues, when medicines are not affordable for patients, because of high prices and a lack of health plans to reimburse them. Orphan drug regulations do not address this issue. On the contrary, it has been shown that liberty of pricing for rare disease products contribute to access deficits and to debates on the effectiveness of orphan drug regulations even in affluent developed countries, in which these regulations apply. Remedying economic access deficits, however, is one of the pillars of the draft Medical Research and Development Treaty which raises the question if, and how, access deficits could be operationalized if they were to become a criterion to determine the neglect of a certain disease.

Prevalence and burden of disease were also named as criteria for a definition of neglected diseases. We assume that in the context of this question, prevalence and burden of disease are synonymous to high prevalences and high burden of disease. Some aspects may have to be considered if these items were to serve as criteria for a definition. It has been shown that, owing to the infrastructural situation in many endemic countries, data on prevalences often do not reflect true prevalence rates. Furthermore, if prevalence were a criterion for the definition of a neglected disease, prevalence limits or ranges would have to be set, prompting the questions whether a neglected disease is always a highly prevalent disease, and what does highly prevalent mean in numbers? The Médecins sans Frontiers (MSF) / Drugs for Neglected Diseases (DND) working group concluded that "[…] nobody knows the exact incidence of sleeping sickness, the exact mortality of malaria, or where exactly Buruli ulcer is prevalent. The figures we have are useful because they give an estimate, but that is exactly what they are, (gu)estimates. Basing all decisions on these figures induces the risk of creating false guarantees of objectivity." (Depoortere & Legros, 2001, p. 47)

In the list of criteria for a definition of neglected diseases, disease severity received the lowest ranking in the category "most important"; this may echo the debate about difficulties in using DALYs to properly measure disability from or co-morbidity of neglected diseases. Since disease severity also included the aspect 'life-threatening', the lower ranking for this item in relation to the other items may also be an expression of caution not to allow low mortality rates to de-prioritize medical R&D

activities for neglected diseases. The fourth criterion in the list, i.e. the economic situation of affected populations, describes what has been labeled 'neglected communities'. Neglected diseases are diseases of poverty, seen from the perspective of their causes as well as from the perspective of their lack of available treatments, or access to existing treatments. A strict separation of both perspectives does not seem possible, as has also become apparent in the discussion of the causes for the R&D, or treatment deficit. A criterion labeled 'economic situation of affected populations' will include the issue of market failure for medical R&D as well as the social determinants which cause the burden of neglected diseases in the endemic countries. Consequently, numerous indicators would be required to operationalize this criterion with a view to including it into a definition of neglected diseases. Lastly, the lack of awareness and visibility, which characterizes rare as well as neglected diseases, was named important by the survey respondents to define a neglected disease. Perhaps because of the volatility of such indicators, a lack of awareness and visibility is not considered a measurable criterion for rare diseases in orphan drug regulations. Publications have been used as surrogate parameters to measure the visibility of rare or neglected diseases. The statutory report of 2005 about the performance of the European orphan drug regulation noted an increase in the visibility of orphan diseases, following the regulation's implementation, manifest in a rising number of publications and a growing network of experts. Similarly, in their effort to define the concept of neglected diseases, the Médecins sans Frontiers (MSF) / Drugs for Neglected Diseases (DND) working group included the number of publications as well as the number of people who worked on a specific disease in their list of parameters. Troullier et al. (2002) illustrated, however, that advances in basic research for leishmaniasis and trypanosomes, manifest in relevant publications, had not translated into new products for these diseases. A growing number of publications or people working on a specific disease may thus testify to an increasing visibility and awareness, but this will not necessarily translate into the development of treatments. Hence, a criterion which referred to the awareness and visibility of neglected diseases, will require a set of indicators which document long-term involvement and specific outcomes, such as marketed drugs, or document the (dis)continuation of published projects or of disease-related working groups, including, in case of discontinuation, the identification of relevant reasons.

To conclude, 'neglect' is a very multifaceted concept in relation to tropical infectious diseases. If the need for the development of relevant indicators to establish a definition of neglected diseases arises, *i.a.* for a regulatory instrument, the Delphi method could be a suitable tool to assist in this process.

> *[…] "the resources and know-how exist to save millions of lives." (WHO, 2010g, p. ix) […]": the concept of 'neglect' is confined to the history of public health."(WHO, 2010g, p. 7)*

6.3 Summary of Results and Conclusion

The aim of a Policy Delphi is to gather as many perspectives to an issue as possible to ensure that all relevant aspects will be taken into account in political decision making. As Turoff predicted in his writings about the Policy Delphi, the questionnaire expanded considerably between the first and the second round of our survey. We are very grateful to all survey respondents for their participation in this project. Unfortunately, the scope of this project did not allow us to discuss all items of the questionnaire in detail, and we will continue to analyze the data which the survey respondents contributed.

The presence and the neglect of tropical infectious diseases cannot be attributed to a single cause, nor can it be remedied by a single measure. The outcome of the question on likely causes for the R&D and treatment deficit in our survey reflected the findings and arguments of WHO reports and other relevant publications, which attribute the R&D deficit for neglected diseases to market failure and to a lack of public and private investment. In the course of the survey, and from the suggestions for additional causes which the respondents contributed, it became apparent that it was difficult to separate the causes for the R&D deficit from the causes for the prevalence of neglected diseases, and the lack of access to treatment. The contributions by the participating stakeholders emphasized once more that health in developing countries will not be improved by promoting biomedical research and development alone. Poverty, both as a reason for market failure and as disease-proliferating factor, became the most

important cause in the second round. High rankings were also given to inadequate health systems, inadequate research infrastructure and the lack of access to treatments in endemic countries. These rankings support any shift in focus from vertical, disease-related programs to a comprehensive public health strategy, including intersectoral and population-based approaches, the strengthening of health systems, from local delivery infrastructure to national social security systems, and fostering an approach of 'health in all policies'. (cf. Kickbusch, 2010b; Ault, 2008; Ehrenberg & Ault, 2005; Hein, 2007)

The majority of the survey participants advocated a regulatory instrument to promote R&D into neglected diseases. With their comments, they expressed the hope that such an instrument will not only encompass funding flows for R&D, but also be dedicated to increasing international research cooperation and building relevant capacity in endemic countries. The draft Medical Research and Development Treaty explicitly includes these objectives, while orphan drug acts have promoted cooperation and network building among experts and with patient organizations. Substantial differences between orphan drug acts and the draft Medical Research and Development Treaty precluded a comparative analysis of the performance of both instruments. Still, if the priorities of both instruments were to be compared, one may conclude that orphan drug acts compensate structural R&D deficits, while the MRDT aims to correct them. Current push incentives of orphan drug acts were considered desirable and feasible to promote R&D into neglected diseases; their adaptation to the needs of neglected disease product development on the basis of a structured needs-assessment among stakeholders could be a next step. Orphan drug pull-incentives do not compensate for the market failure for neglected diseases. If the infrastructure of orphan drug acts were to be used for neglected diseases, proper pull-mechanisms could be installed under orphan drug acts, such as prize-funds on the basis of health impact and with the aim of ensuring patients' access to new products. We anticipate that such a step to amend and extend orphan drug acts would prompt another discussion about market exclusivity for rare disease products, about access and the prices of orphan products. This must not be for the worse, however. The drafting of the European regulation on rare diseases took account of shortcomings that had been identified in the process of implementing the U.S. Orphan Drug Act, on which it was partly modeled. By

the same logic, and in view of the most recent developments, an extension of orphan drug regulations to neglected diseases could equally stimulate a review of the regulation, taking into account public health concerns voiced so far, and addressing aspects such as access to orphan products, or the pricing of products which are developed with public funding. The envisaged international medical R&D treaty will focus on R&D needs for patients in developing countries. Perhaps, in the long run, the change of paradigm which it initiated could benefit rare diseases as well as neglected diseases, and both orphan drug regulations and a Medical Research and Development Treaty will complement each other for the benefit of both patient groups.

7 List of References

(1) Aagaard-Hansen J& Chaignat CL. (2010): Neglected tropical diseases: equity and social determinants. In: Blas E, Kurup AS, editors: Equity, social determinants and public health programmes. World Health Organization

(2) Akins R et al. (2005): Stability of response characteristics of a Delphi panel: application of bootstrap data expansion. BMC Medical Research Methodology 5, doi:10.1186/1471-2288-5-37

(3) Ammon U (2005): Quantitative Methoden der Organisationsforschung. Delphi-Befragung. http://www.qualitative-research.net/organizations/2/or-db-d.htm, Accessed 26.5.2006

(4) Anderson G (2009): Spurring new research for neglected diseases. Health Aff (Millwood) 28 (6), 1750-1759

(5) Ault SK (2008): Intersectoral approaches to neglected diseases. Annals of the New York Academy of Sciences 1136, 64-69

(6) Aymé S& Schmidtke J (2007): Networking for rare diseases: a necessity for Europe. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz 12, 1477-1483

(7) Baker D (2004): Financing Drug Research: What Are the Issues? Issue Brief. Center for Economic and Policy Research (CEPR), Washington, D.C., http://www.cepr.net/documents/publications/intellectual_property_2004_09.pdf, Accessed 24.5.2012

(8) Behnke J et al. (2006): Empirische Methoden der Politikwissenschaft. Verlag Ferdinand Schöningh, Paderborn,

(9) Berndt ER et al. (2007): Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. Health Econ 16, 491-511

(10) Beywl W& Schepp-Winter E (2000): Zielgeführte Evaluation von Programmen - ein Leitfaden. QS Materialien zur Qualitätssicherung in der Kinder- und Jugendhilfe. Bundesministerium für Familie, Senioren, Frauen und Jugend: Bonn., http://www.univation.org/download/QS_29.pdf, Accessed 23.5.2012

(11) BMZ (2009): Gesundheit und Menschenrechte. BMZ SPEZIAL 162. Bundesministerium für wirtschaftliche Zusammenarbeit und Entwicklung. Bonn.

(12) Bührlen B et al. (2003): New Products and Services. Analysis of Regulations Shaping New Markets. Third Interim Report. Part B: The Impact of Regulation on the Development of New Products in the Pharmaceutical Sector. Fraunhofer Institute. Systems and Innovation Research. Karlsruhe. http://isi.fraunhofer.de/isi-media/docs/isi-publ/2003/isi03b70/case-study-pharma.pdf, Accessed 23.5.2012

(13) Callan B& Gillespie I (2007): The path to new medicines. Nature 449 (7159), 164-165

(14) Canning D (2006): Priority setting and the 'neglected' tropical diseases. Trans R Soc Trop Med Hyg 100 (6), 499-504

(15) Chokshi DA (2008): Needs-based research and development. Health Aff (Millwood) 27 (1), 302

(16) Clarke JT (2006): Is the current approach to reviewing new drugs condemning the victims of rare diseases to death? A call for a national orphan drug review policy. CMAJ 174 (2), 189-190

(17) Cohen-Kohler J (2007): The Morally Uncomfortable Global Drug Gap. Clinical Pharmacology & Therapeutics 82 (5), 610-614

(18) Coleman CH et al. (2008): The contribution of ethics to public health. Bull World Health Organ 86 (8), 578-57A

(19) Conteh L et al. (2010): Socioeconomic aspects of neglected tropical diseases. Lancet 375 (9710), 239-247

(20) Correa CM (2006): Implications of bilateral free trade agreements on access to medicines. Bull World Health Organ 84 (5), 399-403

(21) Costa Chaves G& Oliveira MA (2007): A proposal for measuring the degree of public health-sensitivity of patent legislation in the context of the WTO TRIPS Agreement. Bulletin of the World Health Organization 85 (1), 49-56

(22) Council of the European Union (2009): Council Recommendation of 8 June 2009 on an action in the field of rare diseases. Official Journal of the European Union (209/C 151/02), C 151-7-C 151/10

(23) CPTech (2005a): CPTech Letter concerning "Request to Evaluate Proposal for New Global Medical R&D Treaty". http://www.who.int/intellectualproperty/submissions/CPTech.pdf, 23.5.2012a

(24) ----- (2005b): Medical Research and Development Treaty (MRDT). Discussion draft 4. http://www.cptech.org/workingdrafts/rndtreaty4.pdf, 23.5.2012b

(25) Daar A et al. (2007): Grand challenges in chronic non-communicable diseases. The top 20 policy and research priorities for conditions such as diabetes, stroke and heart disease. Nature 450 (7169), 494-496

(26) Dalkey N (1969): An experimental study of group opinion. The Delphi Method. Futures 1 (5), 408-426

(27) Danzon PM (2007): At what price? Nature 449 (7159), 176-179

(28) Day J& Bobeva M (2005): A Generic Toolkit for the Successful Management of Delphi Studies. The Electronic Journal of Business Research Methodology 3 (2), 103-116

(29) de Meyrick J (2003): The Delphi method and health research. Health Education 103 (1), 7-16

(30) de Villiers MR et al. (2005): The Delphi technique in health sciences education research. Med Teach 27 (7), 639-643

(31) Dear JW et al. (2006): Are rare diseases still orphans or happily adopted? The challenges of developing and using orphan medicinal products. Br J Clin Pharmacol 62 (3), 264-271

(32) Denis A et al. (2009): Policies for Orphan Diseases and Orphan Drugs. Health Technology Assessment (HTA). KCE reports 112C (D/2009/10.273/32). Belgian Health Care Knowledge Centre (KCE). KCE reports 112C (D/2009/10.273/32). Brussels.

(33) Dentico N& Ford N (2005): The courage to change the rules: a proposal for an essential health R&D treaty. PLoS Med 2 (2), e14

(34) Department of Health and Human Services - Office of Inspector General (2001): The Orphan Drug Act. Implementation and Impact. OEI-09-00-00380 http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf, Accessed 23.5.2012

(35) Depoortere E& Legros D (2001): Developing a Needs-Based and Rational Approach to Identify Neglected Diseases and Select R&D Projects that Could Maximally Impact Treatment Options. Médecins Sans Frontières/Ärzte ohne Grenzen e.V. http://archives.who.int/prioritymeds/report/append/nd_apx_1.pdf, Accessed 23.5.2012

(36) DiMasi J& Grabowski H (2004): Patens and R&D Incentives: comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D. Submission to the WHO Commission on Intellectual Property, Innovation and Public Health. http://www.who.int/intellectualproperty/news/en/Submission3.pdf, Accessed 23.5.2012

(37) ----- (2007): Should the Patent System for New Medicines be Abolished. Clinical Pharmacology & Therapeutics 82 (5), 488-490

(38) DiMasi J et al. (2003): The price of innovation: new estimates of drug development costs. J Health Econ 22 (2), 151-185

(39) Drummond MF et al. (2007): Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care 23 (1), 36-42

(40) EBE / The European Association for Bioindustries (EuropaBio) (2005): Towards an Optimal Orphan Medicinal Products (OMP) Framework in Europe. Orphan drugs White Paper. Biotechnolgy Law Report 24 (3), 370-381

(41) Ehrenberg JP& Ault SK (2005): Neglected diseases of neglected populations: thinking to reshape the determinants of health in Latin America and the Caribbean. BMC Public Health 5, 119

(42) EMA (2005): COMP Report to the Commission in relation to Article 10 of Regulation 141/2000 on Orphan Medicinal Products. Doc. Ref. EMEA/35218/2005 Final. European Medicines Agency. London.

(43) ----- (2006): Annual Report of the European Medicines Agency 2005. European Medicines Agency. London.

(44) ----- (2010a): Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation. EMA/COMP/15893/2009 Final. European Medicines Agency, London

(45) ----- (2010b): Road Map to 2015. The European Medicines Agency's contribution to science, medicines and health. European Medicines Agency. London.

(46) ----- (2011): Medicines for rare diseases. www.ema.europa.eu, Accessed 23.1.2011

(47) EMEA (2002): Seventh Annual Report 2001. The European Agency for the Evaluation of Medicinal Products. London.

(48) ----- (2003): Eights Annual Report 2002. The European Agency for the Evaluation of Medicinal Products. London.

(49) Enzmann H& Lütz J (2008): Förderung von Arzneimitteln für seltene Leiden durch die Europäische Gemeinschaft. Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz 51, 500-508

(50) European Commission (1998): Proposal for a European Parliament and Council Regulation (EC) on orphan medicinal products (presented by the Commission). COM (1198) 450 final.

(51) European Commission. Commission Regulation (EC) No 847/2000 of 27 April 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 No. L 103, 22/01/200027-4-2000.

(52) ----- (2006a): Commission Staff Working Document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained. Document on the basis of Article 10 of Regulation (EC) No 141/2000. Sec(2006) 832

(53) ----- (2006b): Inventory of Community and Member States's incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005. http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf, Accessed 23.5.2012b

(54) ----- (2006c): The FOR-LEARN Online Foresight Guide. http://forlearn.jrc.es/guide/2_design/meth_delphi.htm, Accessed 23.5.2012c

(55) ----- (2008a): Communication from the European Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. COM(2008) 679 final

(56) ----- (2008b): Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity or orphan medicinal products. Official Journal of the European Union (2008/C 242/07), C 242-8-C 242/11

(57) European Parliament (2005): Report on Major and Neglected Diseases in Developing Countries (2005/2047(INI)). FINAL A6-0215/2005

(58) European Parliament and Council (2004): 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. Official Journal of the European Union, L 136-1-L 136/33

(59) European Parliament and European Council (2000): Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Official Journal of the European Union, L18-1-L18/5

(60) EURORDIS (2009): The Voice of 12,000 Patients. Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe. http://www.eurordis.org, Accessed 23.5.2012

(61) Farlow A (2007): A Global Medical Research and Development Treaty. An answer to global health needs? IPN Working Papers on Intellectual Property, Innovation and Health. http://www.policynetwork.net/sites/default/files/Global_Medical_Research_web.pdf, Accessed 23.5.2012

(62) Faunce TA& Nasu H (2008): Three Proposals for Rewarding Novel Health Technologies Benefiting People Living in Poverty. A Comparative Analysis of Prize Funds, Health Impact Funds and a Cost-Effectiveness/Competitive Tender Treaty. Public Health Ethics 1 (2), 146-153

(63) Fehr A et al. (2011a): Delphi expert survey on promoting research and development into drugs for neglected diseases. (Abstract). Tropical Medicine & International Health 16 (Supp. 1), 329-330

(64) ----- (2011b): Expert Delphi survey on research and development into drugs for neglected diseases. BMC Health Serv Res 11, 312

(65) GAVI Alliance (2007): Q&A: Advance Market Commitments (AMCs). http://www.stoptb.org/assets/documents/about/cb/meetings/13/2.07-05%20Advance%20Market%20Commitments/2.07-05.1%20AMC%20Q&A.pdf, Accessed 10.6.2012

(66) Geyer S& Siegrist J. (2003): Sozialwissenschaftliche Verfahren in den Gesundheitswissenschaften. In: Hurrelmann K, Laaser U, editors: Handbuch Gesundheitswissenschaften. Juventa Verlag, Weinheim und München. 259-279

(67) Global Forum for Health Research. (2010): "10/90 gap". http://www.globalforumhealth.org/about/1090-gap/, Accessed 23.5.2012

(68) Grabowski H (2005): Encouraging the development of new vaccines. Health Aff (Millwood) 24 (3), 697-700

(69) Häder M (2000): Die Expertenauswahl bei Delphi-Befragungen. http://www.gesis.org/fileadmin/upload/forschung/publikationen/gesis_reihen/howto/how-to5mh.pdf, Accessed 28.5.2012

(70) -----. (2002): Delphi Befragungen. Ein Arbeitsbuch. Westdeutscher Verlag GmbH, Wiesbaden,

(71) Haffner ME (1991): Orphan products: origins, progress, and prospects. Annu Rev Pharmacol Toxicol 31, 603-620

(72) Haffner ME et al. (2008): Does orphan drug legislation really answer the needs of patients? Lancet 371 (9629), 2041-2044

(73) Haffner ME et al. (2002): Two decades of orphan product development. Nat Rev Drug Discov 1 (10), 821-825

(74) HAI (2010): Open Letter to the Members of the Executive Board of the World Health Organization. http://www.haiweb.org/ei_ip_updates/15%20Jan%202010%20Open%20letter%20to%20WHO%20Executive%20Board%20on%20EWG%20&%20GSPA%20implementation%20%28EN%29.pdf, Accessed 23.5.2012

(75) Hampel D (2004): Armut und Armutsbekämpfung. Teil 2: Manifestationen und Dimensionen der Armut. InWEnt - Internationale Weiterbildung und Entwicklung gGmbH. Abteilung Gesundheit/Ärzteprogramm, Bonn

(76) Hein W& Kickbusch I (2010): Weltgesundheit:die Suche nach Effizienz im Labyrinth der Akteure. GIGA German Institute of Global and Area Studies - Leibniz-Institut für Globale und Regionale Studien, Hamburg

(77) Hein W (2007): Kompass 2020. Deutschland in den internationalen Beziehungen. Ziele, Instrumente, Perspektiven. Friedrich-Ebert-Stiftung, Bonn/Berlin

(78) Helmer O (1977): Problems in futures research: Delphi and causal cross-impact analysis. Futures 9 (1), 17-31

(79) Herrling P (2007): Patent sense. Nature 449 (7159), 174-175

(80) Hogerzeil H (2005): Essential medicines for rare diseases. Abstract. 1st International Conference on Rare Diseases and Orphan Drugs (ICORD 2005). http://icord.se/documents/pdf/programme_abstracts.pdf, 18.6.2012

(81) Hopkins AL et al. (2007): Mission possible. Nature 449 (7159), 166-169

(82) Hotez P et al. (2009): Rescuing the bottom billion through control of neglected tropical diseases. Lancet 373 (9674), 1570-1575

(83) Hotez P et al. (2006): Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med 3 (5), e102

(84) Hotez P et al. (2010): National summit on neglected infections of poverty in the United States. Emerg Infect Dis 16 (5), e1

(85) Hubbard T& Love J (2004): A new trade framework for global healthcare R&D. PLoS Biol 2 (2), E52

(86) Hunt P. (2007): Neglected diseases: A human rights analysis. Special Topics No. 6 ed. World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases,

(87) Interagency Task Force to the Secretary of Health EaW (1979): Interagency Task Force Report on Significant Drugs of Limited Commercial Value. http://rarediseases.info.nih.gov/files/1979_Interagency_Task_Force_Report_on_Significant_Drugs_of_Limited_Clinical_Value.pdf, Accessed 23.5.2012

(88) Jayasinghe KS et al. (1998): Ethics of resource allocation in developing countries: the case of Sri Lanka. Soc Sci Med 47 (10), 1619-1625

(89) Kelle Udo& Kluge Susanne. (1999): Vom Einzelfall zum Typus. Fallvergleich und Fallkontrastierung in der qualitativen Sozialforschung. Leske + Budrich, Opladen,

(90) Kickbusch I (2005): Tackling the political determinants of global health. BMJ 331 (7511), 246-247

(91) ----- (2010a): Gruppentherapie. Strategien der Seuchenbekämpfung. Internationale Politik 4 (Juli/August 2010), 46-52

(92) ----- (2010b): Health in all policies: where to from here? Health Promot Int 25 (3), 261-264

(93) Knight AW& Senior TP (2006): The common problem of rare disease in general practice. Med J Aust 185 (2), 82-83

(94) Krebs J (2008): The importance of public-health ethics. Bull World Health Organ 86 (8), 579

(95) Leis García A (2004): Is the Copy Better than the Original? The Regulation of Orphan Drugs: a US-EU Comparative Perspective. http://leda.law.harvard.edu/leda/search/toc.php3?handle=HLS.Library.Leda/leis_garciaa-is_copy_better, Accessed 23-5-2012

(96) Liese B et al. (2010): Programmes, partnerships, and governance for elimination and control of neglected tropical diseases. Lancet 375 (9708), 67-76

(97) Light DW (2009): Advance Market Commitments. Current Realities and Alternate Approaches. Health Action International (HAI); Medico International. Amsterdam, Frankfurt.

(98) Liikanen E (2002): Round Table on lack of R&D for neglected diseases: Challenges to combat neglected diseases. Speech of the Member of the EU-Commission. http://www.timeshighereducation.co.uk/story.asp?storyCode=171668&sectioncode=26, Accessed 23.5.2012

(99) Linstone HA& Turoff ME. (2002): The Delphi Method: Techniques and Applications. http://is.njit.edu/pubs/delphibook/, Accessed 23-5-2012

(100) Lob-Levyt J& Schaaber J (2009): Private Geber im Gesundheitswesen. http://www.welt-sichten.org/artikel/art-04-009/cm/private-geber-im-gesundheitswesen.html, Accessed 23.5.2012

(101) López Montaño C (2010): Open Letter to the WHO EB from Cecilia López Montaño, EWG member. http://keionline.org/node/756

(102) Love J. (1999): Brief Note on the abuse of Orphan Drug programs in creating monopolies. http://www.cptech.org/ip/health/orphan/#Brief note on the abuse of Orphan Drug programs in creating monopolies, Accessed 23.5.2012

(103) Love J& Hubbard T (2007): The Big Idea: Prizes to Stimulate R&D for new Medicines. Knowledge Ecology International, http://www.keionline.org/misc-docs/bigidea-prizes.pdf;

(104) Luppe T& Kreischer S Médecins Sans Frontières/Ärzte ohne Grenzen e.V., editor (2004): Patentschutz und die Zukunft des Medikamentenzugangs in ärmeren Ländern. http://www.aerzte-ohne-grenzen.de/kennenlernen/veroeffentlichungen/dokumente-zum-herunterladen/publikationen-medikamentenkampagne/index.html, Accessed 23.5.2012

(105) Marshall T (2005): Orphan drugs and the NHS: consider whom drug regulation is designed to protect. BMJ 331 (7525), 1144

(106) Médecins sans Frontières (MSF) (2005): Amendment to WTO TRIPS Agreement makes access to affordable medicines even more bleak. Press Release. http://www.msfaccess.org/about-us/media-room/press-releases/amendment-wto-trips-agreement-makes-access-affordable-medicines, 23.5.2012

(107) ----- (2007): The effects of the 2005 TRIPS implementation deadline on access to medicinces. http://www.msfaccess.org/sites/default/files/MSF_assets/Access/Docs/ACCESS_briefing_EffectsTRIPS-Implementation_ENG_2005.pdf, Accessed 23.5.2012

(108) Médecins sans Frontières (MSF)& Drugs for Neglected Diseases Initiative Médecins sans Frontières/Drugs for Neglected Diseases Working Group (MSF/DND) (Eds.), editor (2001): Tödliches Ungleichgewicht: Die Krise in Forschung und Entwicklung von Arzneimitteln gegen vernachlässigte Krankheiten.

(109) Milne C et al. (2001): Orphan Drug Laws in Europe and the US: Incentives for the Research and Development of Medicines for the Diseases of Poverty. CMH Working Paper Series, Paper No. WG2: 8. WHO Commission on Macroeconomics and Health.

(110) Molyneux DH (2004): "Neglected" diseases but unrecognised successes--challenges and opportunities for infectious disease control. Lancet 364 (9431), 380-383

(111) Molyneux DH et al. (2005): "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Medicine 2 (11), e336

(112) Moran M et al. (2011): G-Finder 2010. Global Funding of Innovation for Neglected Diseases. Neglected disease research and development: Is the Global Financial Crisis Changing R&D? Policy Cures. London International Development Centre.

(113) Moran M et al. (2009a): Neglected Disease Research & Development: New Times, New Trends. G-Finder 2009. G-Finder. The George Institute for International Health. Australia / United Kingdom.

(114) Moran M et al. (2009b): Neglected Disease Research and Development: How Much Are We Really Spending? PLoS Med 6 (2), e30

(115) Moran MK et al. (2009c): Neglected diseases research & development: How much are we really spending? G-Finder 2008. Health Policy Division, The George Institute for International Health. Australia / United Kingdom.

(116) Moran MK et al. (2005): The new landscape of neglected disease drug development. Pharmaceutical R&D Policy Project. The London School of Economics and Political Science. The Wellcome Trust. London.

(117) Mullen PM (2003): Delphi: myth and reality. Journal of Health Organization and Management 17 (1), 37-52

(118) National Organization for Rare Disorders. (2007): About NORD. http://www.rarediseases.org/about, Accessed 23.5.2012

(119) Niedrig M et al. (2006): Steckbriefe seltener und importierter Infektionskrankheiten. Robert Koch-Institut. Berlin.

(120) Niens LM et al. (2010): Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world. PLoS Med 7 (8)

(121) NIH (2009): NIH Announces New Program to Develop Therapeutics for Rare and Neglected Diseases. http://www.nih.gov/news/health/may2009/nhgri-20.htm, Accessed 30.5.2012

(122) O'Loughlin R& Kelly A (2004): Equity in resource allocation in the Irish health service: A policy Delphi study. Health Policy 67 (3), 271-280

(123) OrphaNet (2010a): About Orphan Drugs. http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN, Accessed 23.5.2012a

(124) ----- (2010b): Lists of Orphan Drugs in Europe. Orphanet Report Series. Orphan Drugs collection. http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf, Accessed 23.5.2012b

(125) ----- (2010c): Worldwide Comparison of Regulation. http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_COMPARISON, Accessed 23.5.2012c

(126) Orsenigo L (2005): Review of CPTech Proposal for an R&D Treaty. Submission to the WHO Commission on Intellectual Property, Innovation and Public Health. http://www.who.int/intellectualproperty/submissions/orsenigo_comments.pdf, Accessed 23.5.2012

(127) Owen A et al. (2008): A new model to evaluate the long-term cost effectiveness of orphan and highly specialised drugs following listing on the Australian Pharmaceutical Benefits Scheme: the Bosentan Patient Registry. J Med Econ 11 (2), 235-243

(128) Pakes BN (2006): Public health ethics and intellectual property policy. Bull World Health Organ 84 (5), 341

(129) Pécoul B (2004): New drugs for neglected diseases: from pipeline to patients. PLoS Med 1 (1), e6

(130) Pécoul B et al. (1999): Access to essential drugs in poor countries: a lost battle? JAMA 281 (4), 361-367

(131) Pill J (1971): The Delphi Method: Substance, Context, A Critique and an Annotated Bibliography. Socio-Econ Plan Sci 5, 57-71

(132) Pogge T (2005): Human rights and global health: a research program. Metaphilosophy 36 (1/2), 182-209

(133) Prodi R (2003): Round Table on Access to Medicines. Speech of the President of the EU-Commission, Romano Prodi. Brussels, April 28, 2003. http://europa.eu/rapid/pressReleasesAction.do?reference=SPEECH/03/215&format=HTML&aged=0&language=EN&guiLanguage=en, Accessed 23.5.2012

(134) Razum O et al. (2006): Globalisierung-Gerechtigkeit-Gesundheit. Verlag Hans Huber, Hogrefe AG, Bern,

(135) Rep Waxman HA (26.4.1990): Orphan Drug Amendments of 1990. H.R.4638. http://thomas.loc.gov/cgi-bin/bdquery/z?d101:HR04638:@@@L&summ2=m& Accessed 23.5.2012.

(136) ----- (24.3.1994): Orphan Drug Act Amendments of 1994. H.R.4160. http://www.gpo.gov/fdsys/pkg/BILLS-103hr4160ih/pdf/BILLS-103hr4160ih.pdf Accessed 23.5.2012.

(137) Ridley DB& Sanchez AC (2010): Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. Lancet 376 (9744), 922-927

(138) Ridley DB et al. (2006): Developing Drugs For Developing Countries. Health Aff 25 (2), 313-324

(139) Robinson M (2007): The value of a human rights perspective in health and foreign policy. Bulletin of the World Health Organization 85 (3), 241-242

(140) Roche Pharmaceuticals (2003): Engagement für einen weltweit besseren Zugang zur medizinischen Versorgung. http://www.roche.com/pages/downloads/sustain/pdf/comm_diff_rep_d.pdfm, Accessed 23.5.2012

(141) Rogoyski R (2006): The Orphan Drug Act and the Myth of the exclusivity incentive. Colum Sci & Tech L Rev 7 (4), 1-22

(142) Sackman H. (1975): Delphi Critique. Expert Opinion, Forecasting and Group Process. The Rand Corporation. Lexington Books D.C. Heath and Company. Lexington, Massachusetts. Toronto. London,

(143) Schaaber J& Wagner-Ahlfs C (2011): Forschung für vernachlässigte Krankheiten. Plädoyer für eine nachhaltige öffentliche Förderung. PHARMA-BRIEF *SPEZIAL*. Ärzte ohne Grenzen; BUKO Pharma-Kampagne; Evangelischer Entwicklungsdienst; Universities Allied for Essential Medicines Germany. Gesundheit und Dritte Welt e.V., Bielefeld.

(144) Scholles F. (2006): Planungsmethoden: Delphi. www.laum.uni-hannover.de/ilr/lehre/Ptm/Ptm_KreaDelphi.htm, Accessed 23.5.2012

(145) Schopper D et al. (2000): When providers and community leaders define health priorities: the results of a Delphi survey in the canton of Geneva. Soc Sci Med 51 (3), 335-342

(146) Seoane-Vazquez E et al. (2008): Incentives for orphan drug research and development in the United States. Orphanet J Rare Dis 3, 33

(147) Spiegel JM et al. (2010): Which New Approaches to Tackling Neglected Tropical Diseases Show Promise? PLoS Med 7 (5), e1000255

(148) Stefanini A (1999): Ethics in health care priority-setting: a north-south double standard? (Editorial). Trop Med Int Health 4, 709-712

(149) Stevens P (2004): Diseases of poverty and the 10/90 Gap. International Policy Network. http://www.fightingdiseases.org/pdf/Diseases_of_Poverty_FINAL.pdf.

(150) Thamer M et al. (1998): A cross-national comparison of orphan drug policies: implications for the U.S. Orphan Drug Act. J Health Polit Policy Law 23 (2), 265-290

(151) Thoene JG (1991): Curing the Orphan Drug Act. Science 251 (4998), 1158-1159

(152) Tren R& Bate R (2006): Government-Controlled Pharmaceutical Research and Development: A Recipe for Desaster. American Enterprise Institute for Public Policy Research, http://www.aei.org/files/2006/05/22/20060522_HPOPOSTED_g.pdf, Accessed 23.5.2012

(153) Trouiller P et al. (1999): Is orphan drug status beneficial to tropical disease control? Comparison of the American and future European orphan drug acts. Trop Med Int Health 4 (6), 412-420

(154) Trouiller P et al. (2002): Drug development for neglected diseases: a deficient market and a public-health policy failure. Lancet 359 (9324), 2188-2194

(155) Trouiller P et al. (2001): Drugs for neglected diseases: a failure of the market and a public health failure? Trop Med Int Health 6 (11), 945-951

(156) Turoff M. (2002): The Policy Delphi. In: Linstone HA, Turoff M, editors: The Delphi Method: Techniques and Applications.

(157) United Nations MDG Gap Task Force (2009): Access to affordable essential medicines. In: Millennium Development Goal 8. Strengthening the Global Partnership for Development in a Time of Crisis. Report 2009New York.

(158) United States Congress. The Orphan Drug Act (as amended). Code of Federal Regulations, Title 21, Volume 5, Revised as of April 1, 2004. 1983.

(159) United States Congress. "Health Promotion and Disease Prevention Amendments of 1984". Public Law 98-551. 30-10-1984.

(160) United States Congress. Orphan Drug Amendments of 1985. Public Law 99-91. 15-8-1985.

(161) United States Congress. Orphan Drug Amendments of 1988. Public Law 100-290. 18-4-1988.

(162) United States Congress. Food and Drug Administration Amendments Act of 2007. Public Law 111-85. 27-9-2007.

(163) Vanderelst D& Speybroeck N (2010): Quantifying the lack of scientific interest in neglected tropical diseases. PLoS Negl Trop Dis 4 (1), e576

(164) Villa S et al. (2009): Orphan drug legislation: lessons for neglected tropical diseases. Int J Health Plann Manage 24 (1), 27-42

(165) Webber D& Kremer M (2001): Perspectives on stimulating industrial research and development for neglected infectious diseases. Bull World Health Organ 79 (8), 735-741

(166) Wellman-Labadie O& Zhou Y (2009): The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity? Health Policy 95 (2-3), 216-228

(167) Wetterauer B& Schuster R (2008): Seltene Krankheiten. Probleme, Stand und Entwicklung der nationalen und europäischen Forschungsförderung. Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz 51, 519-528

(168) WHA. Intellectual property rights, innovation and public health. WHA 56.27. 28-5-2003.

(169) WHA. Establishment of a consultative expert working group on research and development: financing and coordination. WHA 63.28. 21-5-2010.

(170) WHO (2001): Macroeconomics and Health: Investing in Health for Economic Development. Report of the Commission on Macroeconomics and Health. WHO. Geneva, Switzerland.

(171) ----- (2002): Report of the WHO Commission on Macroeconomics and Health. Report by the Director General. Summary. FIFTY-FIFTH WORLD HEALTH ASSEMBLY. Provisional agenda item 13.1. A55/5. WHO. Geneva, Switzerland.

(172) ----- Daumerie D, Kindhauser MK, editors (2004a): Intensified Control of Neglected Diseases. Report of an International Workshop, Berlin, 10-12 December 2003.

(173) -----. (2004b): TDR Disease Portfolio. http://www.who.int/tdr/diseases/default.htm, Accessed 7.4.2006b

(174) ----- (2005): Human Rights, Health and Poverty Reduction Strategies. Health and Human Rights Publications Series. WHO Press, World Health Organization. Geneva, Switzerland.

(175) -----. (2006a): Control of Neglected Tropical Diseases (NTD). http://www.who.int/neglected_diseases/en/, Accessed 29.4.2006a

(176) ----- (2006b): Health and Human Rights activities within WHO. http://www.who.int/hhr/activities/Mapping%20HHRactivities%20in%20WHO%20_for%20website%2012%20Sept%202005_.pdf, Accessed 15.6.2012b

(177) -----. (2006c): Intensified Control of Tropical Diseases. www.who.int/neglected_diseases/en, Accessed 18.1.2006c

(178) ----- (2006d): Neglected Tropical Diseases. Hidden successes, Emerging Opportunities. WHO/CDS/NTD/2006.2

(179) ----- (2006e): Public health, innovation and intellectual property rights. Report of the Commission on Intellectual Property Rights, Innovation and Public Health. WHO. Geneva, Switzerland.

(180) -----. (2006f): World Health Organization / Communicable Diseases Department. http://w3.whosea.org/EN/Section10.htm, Accessed 6.4.2006f

(181) ----- (2007): Global Plan to Combat Neglected Tropical Diseases 2008-2015. WHO/CDS/NTD/2007.3. WHO. Geneva, Switzerland.

(182) ----- (2008): Closing the gap in a generation. Health equity through action on the social determinants of health. Final Report. Executive Summary. Commission on Social Determinants of Health. WHO. Geneva, Switzerland.

(183) WHO. Global strategy and plan of action on public health, innovation and intellectual property. WHA61.21. 24-5-2008.

(184) ----- (2010a): Chagas Disease (American trypanosomiasis). Fact Sheet No. 340. http://www.who.int/topics/chagas_disease/en/, Accessed 24.5.2012a

(185) ----- (2010b): Leprosy. Fact Sheet No. 101. http://www.who.int/mediacentre/factsheets/fs101/en/index.html, Accessed 24.5.2012b

(186) ----- (2010c): Magnitude of the problem. https://www.who.int/leishmaniasis/burden/magnitude/burden_magnitude, Accessed 5.8.2010c

(187) -----. (2010d): Neglected tropical diseases. Frequently asked questions. http://www.who.int/neglected_diseases/faq/en/print.html, Accessed 26.7.2010d

(188) ----- (2010e): Research and Development. Coordination and Financing. Report of the Expert Working Group. WHO. Geneva, Switzerland.

(189) ----- (2010f): The disease and its epidemiology. https://www.who.int/leishmaniasis/disease_epidemiology/en/print.html, Accessed 5.8.2010f

(190) ----- (2010g): Working to overcome the global impact of neglected tropical diseases. First WHO report on neglected tropical diseases. WHO. Geneva, Switzerland.

(191) ----- (2012a): African trypanosomiasis (sleeping sickness). Fact Sheet No. 259. http://www.who.int/mediacentre/factsheets/fs259/en/, Accessed 24.5.2012a

(192) ----- (2012b): Buruli ulcer. http://www.who.int/buruli/en/, Accessed 24.5.2012b

(193) ----- (2012c): Buruli ulcer disease (*Mycobacterium ulcerans* infection). Fact sheet No.199. http://www.who.int/mediacentre/factsheets/fs199/en/index.html, Accessed 23.5.2012c

(194) ----- (2012d): Dengue and dengue haemorraghic fever. Fact Sheet No. 117. http://www.who.int/mediacentre/factsheets/fs117/en/index.html, Accessed 24.5.2012d

(195) ----- (2012e): Lymphatic Filariasis. Fact Sheet No. 102. http://www.who.int/mediacentre/factsheets/fs102/en/html

(196) ----- (2012f): Onchocerciasis (river blindness). http://www.who.int/blindness/partnerships/onchocerciasis_home/en/index.html, Accessed 24.5.2012f

(197) ----- (2012g): Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination. Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. WHO. Geneva, Switzerland.

(198) ----- (2012h): Research on leishmaniasis. http://www.who.int/leishmaniasis/en/, Accessed 24.5.2012h

(199) ----- (2012i): Schistosomiasis. Fact Sheet No. 115. http://www.who.int/mediacentre/factsheets/fs115/en/index.html, Accessed 24.5.2012i

(200) WHO Health statistics and informatics Department (2011): Causes of Death 2008 Summary Tables. Estimates of deaths by cause for the year 2008. WHO, Geneva, Switzerland, http://www.who.int/evidence/bod, Accessed 28.5.2012

(201) Winters DJ (2006): Expanding global research and development for neglected diseases. Bull World Health Organ 84 (5), 414-416

(202) WTO. Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health; Decision of the General Council of 30 August 2003. WT/L/540 and Corr.1. 1-9-2003a.

(203) ----- (2003b): TRIPS and pharmaceutical patents. WTO Fact Sheet. http://www.wto.org/english/tratop_e/trips_e/factsheet_pharm00_e.htm, Accessed 24.5.2012b

8 Annex I – Survey Results

I. Causes for the treatment deficit for neglected diseases

Table 8-1 Causes for the treatment deficit -Round I

Causes for the treatment deficit (Round I) N=159)														
	Count	Row Valid N %	Count	Row Valid N %	Count	Row Valid N %	Count	Row Valid N %	Count	Row Valid N %	Total Row Valid N %	Count	Count	Valid N
	most important		**important**		**unimportant**		**least important**		**no judgment**			**abandoned**	**missing**	
No or insufficient sustainability of public funding for R&D for neglected diseases	48	40,3%	57	47,9%	9	7,6%	1	0,8%	4	3,4%	100,0%	24	16	119
No or inadequate direct public funding for research and development (R&D) for neglected diseases	44	35,2%	75	60,0%	4	3,2%	0	0,0%	2	1,6%	100,0%	24	10	125
No or inadequate incentives for the private sector to invest into R&D for neglected diseases	42	33,9%	61	49,2%	11	8,9%	6	4,8%	4	3,2%	100,0%	24	11	124
No or inadequate private sector investment into R&D for neglected diseases	42	33,6%	73	58,4%	6	4,8%	1	0,8%	3	2,4%	100,0%	24	10	125
No or inadequate access to effective drugs for neglected diseases	40	33,1%	57	47,1%	11	9,1%	10	8,3%	3	2,5%	100,0%	24	14	121
No or inadequate research infrastructure in countries with neglected diseases	36	29,5%	68	55,7%	9	7,4%	8	6,6%	1	0,8%	100,0%	24	13	122
No or ineffective drugs for neglected diseases	24	20,5%	57	48,7%	18	15,4%	10	8,5%	8	6,8%	100,0%	24	18	117

Table 8-2 Causes for the treatment deficit -Round II

Causes for the treatment deficit (Round II) N= 77														
	Count	Row Valid N %	Count	Row Valid N %	Count	Row Valid N %	Count	Row Valid N %	Count	Row Valid N %	Total Row Valid N%	Count	Count	Valid N
	most important		**important**		**unimportant**		**least important**		**no judgment**			**Abandoned**	**missing**	
Poverty as disease-proliferating factor (*i.a.* inadequate prevention, inadequate housing, lack of clean water) in endemic countries	35	57,4%	20	32,8%	4	6,6%	2	3,3%	0	0,0%		12	4	61
Poverty as reason for market failure (perception of no market for drugs, insufficient R&D)	33	55,0%	21	35,0%	3	5,0%	2	3,3%	1	1,7%	100,0%	12	5	60
No or insufficient direct public funding for research and development (R&D) for neglected diseases	34	54,8%	25	40,3%	3	4,8%	0	0,0%	0	0,0%	100,0%	12	3	62
No or insufficient sustainability of public funding for R&D for neglected diseases	33	54,1%	25	41,0%	2	3,3%	1	1,6%	0	0,0%	100,0%	12	4	61
Inadequate research priorities in private sector R&D	30	48,4%	23	37,1%	7	11,3%	2	3,2%	0	0,0%	100,0%	12	3	62
No or inadequate health delivery infrastructure and staff in developing countries	28	45,9%	25	41,0%	6	9,8%	1	1,6%	1	1,6%	100,0%	12	4	61
No or inadequate private sector investment into R&D for neglected diseases	28	45,2%	25	40,3%	3	4,8%	5	8,1%	1	1,6%	100,0%	12	3	62
Lack of health-needs driven priority setting in public funding	27	44,3%	31	50,8%	3	4,9%	0	0,0%	0	0,0%	100,0%	12	4	61
No or inadequate incentives for the private sector to invest into R&D for neglected diseases	26	41,9%	28	45,2%	5	8,1%	2	3,2%	1	1,6%	100,0%	12	3	62
No or inadequate access to effective drugs for neglected diseases	25	41,0%	29	47,5%	3	4,9%	4	6,6%	0	0,0%	100,0%	12	4	61
Lack of awareness /visibility of neglected diseases	20	32,8%	32	52,5%	8	13,1%	1	1,6%	0	0,0%	100,0%	12	4	61
No or ineffective drugs for neglected diseases	18	30,0%	35	58,3%	5	8,3%	2	3,3%	0	0,0%	100,0%	12	5	60
No or inadequate research infrastructure in countries with neglected diseases	17	27,9%	37	60,7%	5	8,2%	2	3,3%	0	0,0%	100,0%	12	4	61
No or inadequate research coordination	5	8,2%	30	49,2%	20	32,8%	4	6,6%	2	3,3%	100,0%	12	4	61
Disease-specific research difficulties (unknown etiology, lack of research material)	3	4,9%	38	62,3%	11	18,0%	7	11,5%	2	3,3%	100,0%	12	4	61

Table 8-3 Causes for the R&D and treatment deficit–Statistics-Round I

Causes for the treatment deficit-Statistics-Round I					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
No or inadequate direct public funding for research and development (R&D) for neglected diseases	123	36	1,7	2,0	0,5
No or inadequate private sector investment into R&D for neglected diseases	122	37	1,7	2,0	0,6
No or inadequate incentives for the private sector to invest into R&D for neglected diseases	120	39	1,8	2,0	0,8
No or insufficient sustainability of public funding for R&D for neglected diseases	115	44	1,7	2,0	0,7
No or ineffective drugs for neglected diseases	109	50	2,1	2,0	0,9
No or inadequate access to effective drugs for neglected diseases	118	41	1,9	2,0	0,9
No or inadequate research infrastructure in countries with neglected diseases	121	38	1,9	2,0	0,8

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

Table 8-4 Causes for the R&D and treatment deficit-Statistics-Round II

Causes for the treatment deficit-Statistics-Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Disease-specific research difficulties (unknown etiology, lack of research material)	59	18	2,4	2,0	0,8
Inadequate research priorities in private sector R&D	62	15	1,7	2,0	0,8
Lack of awareness /visibility of neglected diseases	61	16	1,8	2,0	0,7
Lack of health-needs driven priority setting in public funding	61	16	1,6	2,0	0,6
No or inadequate access to effective drugs for neglected diseases	61	16	1,8	2,0	0,8
No or inadequate health delivery infrastructure and staff in developing countries	60	17	1,7	2,0	0,7
No or inadequate incentives for the private sector to invest into R&D for neglected diseases	61	16	1,7	2,0	0,8
No or inadequate private sector investment into R&D for neglected diseases	61	16	1,8	2,0	0,9
No or inadequate research coordination	59	18	2,4	2,0	0,7
No or inadequate research infrastructure in countries with neglected diseases	61	16	1,9	2,0	0,7
No or ineffective drugs for neglected diseases	60	17	1,9	2,0	0,7
No or insufficient direct public funding for research and development (R&D) for neglected diseases	62	15	1,5	1,0	0,6
No or insufficient sustainability of public funding for R&D for neglected diseases	61	16	1,5	1,0	0,6
Poverty as disease-proliferating factor (i.a. inadequate prevention, inadequate housing, lack of clean water) in endemic countries	61	16	1,6	1,0	0,8
Poverty as reason for market failure (perception of no market for drugs, insufficient R&D)	59	18	1,6	1,0	0,7

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

Table 8-5 Causes for the treatment deficit * Place of residence -Round II

	Causes for the treatment deficit * Place of residence Round II						
		Developed country		Developing country		Threshold country / emerging market	
		Count	Column Valid N %	Count	Column Valid N %	Count	Column Valid N %
Disease-specific research difficulties (unknown etiology, lack of research material)	most important	2	5,3%	1	9,1%	0	0,0%
	important	25	65,8%	7	63,6%	0	0,0%
	unimportant	7	18,4%	1	9,1%	0	0,0%
	least important	2	5,3%	2	18,2%	2	100,0%
	no judgment	2	5,3%	0	0,0%	0	0,0%
Inadequate research priorities in private sector R&D	most important	18	46,2%	7	63,6%	1	50,0%
	important	13	33,3%	4	36,4%	0	0,0%
	unimportant	6	15,4%	0	0,0%	1	50,0%
	least important	2	5,1%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%
Lack of awareness / visibility of neglected diseases	most important	9	23,7%	6	54,5%	0	0,0%
	important	21	55,3%	5	45,5%	2	100,0%
	unimportant	7	18,4%	0	0,0%	0	0,0%
	least important	1	2,6%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%
Lack of health-needs driven priority setting in public funding	most important	16	42,1%	7	63,6%	1	50,0%
	important	20	52,6%	3	27,3%	1	50,0%
	unimportant	2	5,3%	1	9,1%	0	0,0%
	least important	0	0,0%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%
No or inadequate access to effective drugs for neglected diseases	most important	16	42,1%	5	45,5%	1	50,0%
	important	16	42,1%	6	54,5%	0	0,0%
	unimportant	2	5,3%	0	0,0%	1	50,0%
	least important	4	10,5%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%

Table 8-5 continued

	Causes for the treatment deficit * Place of residence Round II						
		Developed country		Developing country		Threshold country / emerging market	
		Count	Column Valid N %	Count	Column Valid N %	Count	Column Valid N %
No or inadequate health delivery infrastructure and staff in developing countries	most important	16	42,1%	7	63,6%	1	50,0%
	important	16	42,1%	2	18,2%	1	50,0%
	unimportant	4	10,5%	2	18,2%	0	0,0%
	least important	1	2,6%	0	0,0%	0	0,0%
	no judgment	1	2,6%	0	0,0%	0	0,0%
No or inadequate incentives for the private sector to invest into R&D for neglected diseases	most important	14	35,9%	6	54,5%	0	0,0%
	important	18	46,2%	5	45,5%	1	50,0%
	unimportant	4	10,3%	0	0,0%	1	50,0%
	least important	2	5,1%	0	0,0%	0	0,0%
	no judgment	1	2,6%	0	0,0%	0	0,0%
No or inadequate private sector investment into R&D for neglected diseases	most important	14	35,9%	8	72,7%	1	50,0%
	important	16	41,0%	3	27,3%	1	50,0%
	unimportant	3	7,7%	0	0,0%	0	0,0%
	least important	5	12,8%	0	0,0%	0	0,0%
	no judgment	1	2,6%	0	0,0%	0	0,0%
No or inadequate research coordination	most important	2	5,3%	2	18,2%	0	0,0%
	important	20	52,6%	5	45,5%	2	100,0%
	unimportant	11	28,9%	3	27,3%	0	0,0%
	least important	3	7,9%	1	9,1%	0	0,0%
	no judgment	2	5,3%	0	0,0%	0	0,0%
No or inadequate research infrastructure in countries with neglected diseases	most important	6	15,8%	7	63,6%	1	50,0%
	important	27	71,1%	3	27,3%	1	50,0%
	unimportant	3	7,9%	1	9,1%	0	0,0%
	least important	2	5,3%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%

Table 8-5 continued

	Causes for the treatment deficit * Place of residence Round II						
		Developed country		Developing country		Threshold country / emerging market	
		Count	Column Valid N %	Count	Column Valid N %	Count	Column Valid N %
No or ineffective drugs for neglected diseases	most important	10	26,3%	3	30,0%	1	50,0%
	important	24	63,2%	5	50,0%	0	0,0%
	unimportant	2	5,3%	2	20,0%	1	50,0%
	least important	2	5,3%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%
No or insufficient direct public funding for research and development (R&D) for neglected diseases	most important	22	56,4%	7	63,6%	1	50,0%
	important	15	38,5%	3	27,3%	1	50,0%
	unimportant	2	5,1%	1	9,1%	0	0,0%
	least important	0	0,0%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%
No or insufficient sustainability of public funding for R&D for neglected diseases	most important	21	55,3%	6	54,5%	1	50,0%
	important	15	39,5%	4	36,4%	1	50,0%
	unimportant	1	2,6%	1	9,1%	0	0,0%
	least important	1	2,6%	0	0,0%	0	0,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%
Poverty as disease-proliferating factor (i.a. inadequate prevention, inadequate housing, lack of clean water) in end	most important	20	52,6%	7	63,6%	1	50,0%
	important	13	34,2%	4	36,4%	0	0,0%
	unimportant	4	10,5%	0	0,0%	0	0,0%
	least important	1	2,6%	0	0,0%	1	50,0%
	no judgment	0	0,0%	0	0,0%	0	0,0%
Poverty as reason for market failure (perception of no market for drugs, insufficient R&D)	most important	18	48,6%	7	63,6%	1	50,0%
	important	16	43,2%	2	18,2%	1	50,0%
	unimportant	2	5,4%	1	9,1%	0	0,0%
	least important	0	0,0%	1	9,1%	0	0,0%
	no judgment	1	2,7%	0	0,0%	0	0,0%

II. Orphan drug regulations for rare diseases

Table 8-6 Familiarity with orphan drug laws

Orphan drug regulations for rare diseases (Round I) N= 159									
	Count	Row Valid N%	Count	Row Valid N%	Count	Row Valid N%	Total Valid Row N%	Valid N	Missing
	Active knowledge of orphan drug laws (through e.g. application for OD status)		**Passive knowledge of orphan drug laws**		**No knowledge about orphan drug laws**				
1. Are your familiar with orphan drug laws?	13	10,3%	60	47,6%	53	42,1%	100,0%	126	33

Table 8-7 Effectiveness of orphan drug laws

	Count	Row Valid N%	Count	Row Valid N%	Count	Row Valid N%	Count	Row Valid N%	Count	Row Valid N%	Total Valid Row N%	Count	Count	Total Valid N
	very effective		**effective**		**ineffective**		**very ineffective**		**no judgment**			**abandoned**	**missing**	
2. How effective do you consider orphan drug laws?	5	7,1%	38	54,3%	12	17,1%	0	0,0%	15	21,4%	100,0%	79	10	70

Table 8-8 Effectiveness of incentives of orphan drug laws

3. How effective are the individual provisions of orphan drug laws?	Count	Row Valid N%	Count	Row Valid N%	Count	Row Valid N%	Count	Row Valid N%	Count	Row Valid N%	Total Row Valid N%	Count	Count	Total Valid N
	very effective		**effective**		**ineffective**		**very ineffective**		**no judgment**			**abandoned**	**missing**	
Fee reduction / Fee waivers	6	8,8%	28	41,2%	16	23,5%	1	1,5%	17	25,0%	100,0%	79	12	68
Protocol assistance	9	13,2%	28	41,2%	10	14,7%	0	0,0%	21	30,9%	100,0%	79	12	68
Tax credits	10	14,5%	33	47,8%	7	10,1%	1	1,4%	18	26,1%	100,0%	79	11	69
Market exclusivity	15	22,1%	23	33,8%	12	17,6%	3	4,4%	15	22,1%	100,0%	79	12	68

Table 8-9 Incentives of Orphan Drug laws-Statistics-Round I

Orphan Drug Incentives-Statistics-Round I					
		Fee reduction / Fee waivers	**Market exclusivity**	**Protocol assistance**	**Tax credits**
N	Valid	51	53	47	51
	Missing*	108	106	112	108
Mean		2,2	2,1	2,0	2,0
Median		2,0	2,0	2,0	2,0
Std. Deviation		0,7	0,9	0,6	0,6

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

III. Measures to promote R&D into neglected diseases

Table 8-10 Desirability of Measures-Round I

Desirability of Measures (Round I) N= 159														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Row N%	Count	Count	Total Valid N
	very desirable		**desirable**		**undesirable**		**very undesirable**			**no judgment**		**abandoned**	**missing**	
Public-private partnerships	61	52,6%	34	29,3%	10	8,6%	2	1,7%	9	7,8%	100,0%	34	9	116
Obligations for national governments to invest into neglected disease R&D	56	48,3%	45	38,8%	8	6,9%	2	1,7%	5	4,3%	100,0%	34	9	116
Open source regulations (e.g. for scientific data / compound libraries)	54	46,6%	49	42,2%	3	2,6%	4	3,4%	6	5,2%	100,0%	34	9	116
Separation of innovation incentives from drug prices	45	38,8%	35	30,2%	5	4,3%	5	4,3%	26	22,4%	100,0%	34	9	116
Prize funds for drug innovation	42	35,6%	52	44,1%	8	6,8%	4	3,4%	12	10,2%	100,0%	34	7	118
Philanthropic spending	38	33,0%	56	48,7%	6	5,2%	1	0,9%	14	12,2%	100,0%	34	10	115
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	31	27,0%	62	53,9%	4	3,5%	1	0,9%	17	14,8%	100,0%	34	10	115
Investment obligations into neglected diseases for drug producers/sellers	30	26,1%	42	36,5%	20	17,4%	8	7,0%	15	13,0%	100,0%	34	10	115
Protocol assistance	30	25,9%	51	44,0%	5	4,3%	0	0,0%	30	25,9%	100,0%	34	9	116
Exemption of drugs from market exclusivity	26	22,8%	36	31,6%	14	12,3%	6	5,3%	32	28,1%	100,0%	34	11	114
Advance market commitments	25	21,7%	53	46,1%	15	13,0%	4	3,5%	18	15,7%	100,0%	34	10	115
Patent pools	24	21,1%	37	32,5%	11	9,6%	4	3,5%	38	33,3%	100,0%	34	11	114
Tiered/differential pricing	20	17,9%	47	42,0%	9	8,0%	4	3,6%	32	28,6%	100,0%	34	13	112
Tax credits	16	14,2%	55	48,7%	7	6,2%	2	1,8%	33	29,2%	100,0%	34	12	113
Existing patent regulations	12	10,3%	21	18,1%	35	30,2%	21	18,1%	27	23,3%	100,0%	34	9	116
Market exclusivity	9	7,8%	22	19,1%	30	26,1%	24	20,9%	30	26,1%	100,0%	34	10	115

Table 8-11 Feasibility of Measures-Round I

Feasibility of Measures (Round I) N= 159														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Total Valid N
	very feasible		**feasible**		**unfeasible**		**very unfeasible**		**no judgment**			**abandoned**	**missing**	
Public-private partnerships	50	46,3%	46	42,6%	4	3,7%	0	0,0%	8	7,4%	100%	37	14	108
Philanthropic spending	48	43,6%	45	40,9%	3	2,7%	0	0,0%	14	12,7%	100%	37	12	110
Protocol assistance	36	32,7%	49	44,5%	2	1,8%	0	0,0%	23	20,9%	100%	37	12	110
Open source regulations (e.g. for scientific data / compound libraries)	34	31,2%	53	48,6%	9	8,3%	3	2,8%	10	9,2%	100%	37	13	109
Obligations for national governments to invest into neglected disease R&D	31	28,2%	46	41,8%	22	20,0%	6	5,5%	5	4,5%	100%	37	12	110
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	29	26,6%	56	51,4%	5	4,6%	1	0,9%	18	16,5%	100%	37	13	109
Tax credits	24	21,8%	44	40,0%	5	4,5%	3	2,7%	34	30,9%	100,0%	37	12	110
Prize funds for drug innovation	23	20,9%	66	60,0%	5	4,5%	1	0,9%	15	13,6%	100,0%	37	12	110
Tiered/differential pricing	18	17,0%	41	38,7%	10	9,4%	0	0,0%	37	34,9%	100,0%	37	16	106
Investment obligations into neglected diseases for drug producers/sellers	16	14,5%	40	36,4%	27	24,5%	12	10,9%	15	13,6%	100,0%	37	12	110
Patent pools	15	13,6%	41	37,3%	8	7,3%	4	3,6%	42	38,2%	100,0%	37	12	110
Advance market commitments	15	13,5%	58	52,3%	13	11,7%	1	0,9%	24	21,6%	100,0%	37	11	111
Separation of innovation incentives from drug prices	14	12,6%	44	39,6%	13	11,7%	7	6,3%	33	29,7%	100,0%	37	11	111
Existing patent regulations	11	10,2%	46	42,6%	18	16,7%	3	2,8%	30	27,8%	100,0%	37	14	108
Market exclusivity	11	10,0%	31	28,2%	23	20,9%	3	2,7%	42	38,2%	100,0%	37	12	110
Exemption of drugs from market exclusivity	9	8,2%	41	37,3%	19	17,3%	3	2,7%	38	34,5%	100,0%	37	12	110

Table 8-12 Desirability of Measures-Round II

Desirability of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Valid N
	very desirable		**desirable**		**undesirable**		**very undesirable**		**no judgment**			**Abandoned**	**Missing**	
International / transcontinental research cooperation involving researchers from developing countries	34	60,7%	22	39,3%	0	0,0%	0	0,0%	0	0,0%	100,0%	18	3	56
Raise awareness among policy makers for the impact of neglected diseases on development	34	60,7%	18	32,1%	2	3,6%	1	1,8%	1	1,8%	100,0%	18	3	56
Building research, technical and regulatory capacity in developing countries	34	59,6%	22	38,6%	0	0,0%	0	0,0%	1	1,8%	100,0%	18	2	57
Neglected disease R&D as priority in relevant European Union funding programs (e.g. FP7)	33	57,9%	23	40,4%	1	1,8%	0	0,0%	0	0,0%	100,0%	18	2	57
Parallel measures to improve access to health care and medicines	33	57,9%	20	35,1%	1	1,8%	0	0,0%	3	5,3%	100,0%	18	2	57
Establishment of an international health-needs driven R&D agenda matched to technological opportunities	32	56,1%	19	33,3%	4	7,0%	0	0,0%	2	3,5%	100,0%	18	2	57
Sharing or transfer of technology to developing countries	30	53,6%	20	35,7%	1	1,8%	1	1,8%	4	7,1%	100,0%	18	3	56
Contribution by foreign donors towards capacity building and strengthening the research infrastructure in developing countries	28	50,9%	23	41,8%	2	3,6%	0	0,0%	2	3,6%	100,0%	18	4	55

Table 8-12 continued

Desirability of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Valid N
	very desirable		**desirable**		**undesirable**		**very undesirable**		**no judgment**			**Abandoned**	**Missing**	
Government support and funds for multilateral efforts (e.g. WHO-TDR)	29	50,9%	24	42,1%	2	3,5%	0	0,0%	2	3,5%	100,0%	18	2	57
Public-private partnerships	28	49,1%	19	33,3%	2	3,5%	4	7,0%	4	7,0%	100,0%	18	2	57
Open source regulations (e.g. for scientific data or compound / molecule libraries)	28	48,3%	20	34,5%	4	6,9%	2	3,4%	4	6,9%	100%	18	1	58
Raising the scientific profile of neglected disease research (better career/publication opportunities)	27	48,2%	24	42,9%	3	5,4%	0	0,0%	2	3,6%	100%	18	3	56
Simplified / fast-track funding procedures	26	48,1%	21	38,9%	5	9,3%	0	0,0%	2	3,7%	100%	18	5	54
Competitive grants to publicly fund research	25	43,9%	31	54,4%	1	1,8%	0	0,0%	0	0,0%	100%	18	2	57
Link between neglected disease R&D and research and clinical care for priority diseases such as HIV, TB or Malaria	25	43,9%	23	40,4%	4	7,0%	0	0,0%	5	8,8%	100%	18	2	57
Include neglected diseases in university curricula	25	43,1%	30	51,7%	2	3,4%	0	0,0%	1	1,7%	100%	18	1	58
Building innovation clusters for low-profit oriented R&D in developing countries	24	42,9%	27	48,2%	1	1,8%	0	0,0%	4	7,1%	100%	18	3	56
Interdisciplinary research cooperation with e.g. veterinary medicine, traditional medicine, epidemiology	24	42,1%	30	52,6%	1	1,8%	0	0,0%	2	3,5%	100%	18	2	57

Table 8-12 continued

Desirability of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Valid N
	very desirable		**desirable**		**undesirable**		**very undesirable**		**no judgment**			**Abandoned**	**Missing**	
Obligation for national governments to invest into neglected disease R&D	23	40,4%	21	36,8%	8	14,0%	1	1,8%	4	7,0%	100%	18	2	57
Educate / inform the public about the individual and societal burden of disease of neglected diseases	22	39,3%	29	51,8%	4	7,1%	1	1,8%	0	0,0%	100%	18	3	56
Separation of innovation incentives from drug prices	21	38,2%	15	27,3%	7	12,7%	3	5,5%	9	16,4%	100%	18	4	55
Exclusive funds for R&D / budgetary set-asides exclusively for purchasing medicines for neglected diseases	20	35,7%	21	37,5%	3	5,4%	1	1,8%	11	19,6%	100%	18	3	56
Exemption of drugs from market exclusivity	20	35,1%	22	38,6%	2	3,5%	5	8,8%	8	14,0%	100%	18	2	57
Incentives for the private sector (e.g. advance market commitments, governmental incentives)	20	35,1%	26	45,6%	6	10,5%	2	3,5%	3	5,3%	100%	18	2	57
Protocol and regulatory advice / assistance to neglected disease R&D projects	19	33,9%	31	55,4%	2	3,6%	0	0,0%	4	7,1%	100%	18	3	56
Prize funds with prizes awarded based on degree of innovation	19	33,9%	20	35,7%	7	12,5%	2	3,6%	8	14,3%	100%	18	3	56
Establishment of public (or affordable) preclinical research facilities	19	33,3%	34	59,6%	2	3,5%	0	0,0%	2	3,5%	100%	18	2	57
Patent pools / more flexible patent laws to improve access to research tools	19	32,8%	25	43,1%	0	0,0%	3	5,2%	11	19,0%	100%	18	1	58

Table 8-12 continued

Desirability of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Valid N
	very desirable		**desirable**		**undesirable**		**very undesirable**		**no judgment**			**Abandoned**	**Missing**	
New alternative juridical instruments which allow governments to foster essential health research and development	18	31,6%	21	36,8%	8	14,0%	1	1,8%	9	15,8%	100%	18	2	57
Establishment of accountability systems for funds received	18	31,6%	30	52,6%	1	1,8%	1	1,8%	7	12,3%	100%	18	2	57
Interconnection between research projects on different neglected diseases	18	31,6%	36	63,2%	2	3,5%	0	0,0%	1	1,8%	100%	18	2	57
Lower private sector influence on R&D priority setting	18	31,6%	18	31,6%	9	15,8%	6	10,5%	6	10,5%	100%	18	2	57
Obligation for the private sector to invest x % of profit made from other drugs/treatments into neglected diseases	18	31,6%	20	35,1%	7	12,3%	5	8,8%	7	12,3%	100%	18	2	57
Development to phase III trials by public laboratories	17	29,8%	31	54,4%	3	5,3%	1	1,8%	5	8,8%	100%	18	2	57
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	16	28,1%	32	56,1%	4	7,0%	0	0,0%	5	8,8%	100%	18	2	57
International regulations regarding the private sector	16	28,1%	27	47,4%	9	15,8%	1	1,8%	4	7,0%	100%	18	2	57
Global funders forum to set priorities	14	24,6%	20	35,1%	11	19,3%	4	7,0%	8	14,0%	100%	18	2	57
Association of biotechnology to health systems for better delivery of goods	13	22,8%	27	47,4%	5	8,8%	1	1,8%	11	19,3%	100%	18	2	57
Tax credits / tax incentives	11	20,4%	25	46,3%	6	11,1%	2	3,7%	10	18,5%	100%	18	5	54

Table 8-12 continued

Desirability of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Valid N
	very desirable		**desirable**		**undesirable**		**very undesirable**		**no judgment**			**Abandoned**	**Missing**	
Royalty arrangements for the benefit of neglected disease R&D if private sector receives exclusive license on government-owned invention for any disease	10	18,2%	18	32,7%	8	14,5%	5	9,1%	14	25,5%	100%	18	4	55
Selective investment (as incentive) in companies which invest in neglected disease R&D	10	18,2%	23	41,8%	12	21,8%	2	3,6%	8	14,5%	100%	18	4	55
Existing patent regulations (e.g. WTO-TRIPS, Doha-Declaration)	10	17,9%	16	28,6%	11	19,6%	6	10,7%	13	23,2%	100%	18	3	56
Abolish patents	9	16,4%	16	29,1%	18	32,7%	6	10,9%	6	10,9%	100%	18	4	55
Private donations to ^real^ pharmaceutical companies to develop drugs for neglected diseases	9	16,1%	15	26,8%	19	33,9%	4	7,1%	9	16,1%	100%	18	3	56
Treaty on cost-effectiveness of new health technologies linked to a competitive tender system	8	14,8%	17	31,5%	7	13,0%	4	7,4%	18	33,3%	100%	18	5	54
Voucher systems in developed markets (as with the FDA) for other products	8	14,3%	14	25,0%	11	19,6%	4	7,1%	19	33,9%	100%	18	3	56
Requirement for developing countries to include research with an adequate budget in all health programs	7	12,5%	32	57,1%	8	14,3%	2	3,6%	7	12,5%	100%	18	3	56

Table 8-12 continued

Desirability of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Valid N
	very desirable		**desirable**		**undesirable**		**very undesirable**		**no judgment**			**Abandoned**	**Missing**	
Reorganize intellectual property rights as intellectual monopoly privileges	6	10,7%	13	23,2%	8	14,3%	11	19,6%	18	32,1%	100%	18	3	56
Market exclusivity	2	3,6%	11	20,0%	20	36,4%	12	21,8%	10	18,2%	100%	18	4	55
Price increases (10-20%) for brandname drugs paid by public health programs to invest this profit in neglected diseases	2	3,6%	5	9,1%	26	47,3%	11	20,0%	11	20,0%	100%	18	4	55

Table 8-13 Feasibility of Measures-Round II

Feasibility of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	Valid N
	definitely feasible		**possibly feasible**		**possibly unfeasible**		**definitely unfeasible**		**no judgment**			**abandoned**	**missing**	
Include neglected diseases in university curricula	34	65,4%	16	30,8%	1	1,9%	0	0,0%	1	1,9%	100,0%	20	5	52
Educate / inform the public about the individual and societal burden of disease of neglected diseases	33	63,5%	15	28,8%	1	1,9%	1	1,9%	2	3,8%	100,0%	20	5	52
Raise awareness among policy makers for the impact of neglected diseases on development	33	63,5%	17	32,7%	1	1,9%	0	0,0%	1	1,9%	100,0%	20	5	52
Public-private partnerships	33	62,3%	16	30,2%	1	1,9%	1	1,9%	2	3,8%	100,0%	20	4	53
Contribution by foreign donors towards capacity building and strengthening the research infrastructure in developing c	29	58,0%	19	38,0%	1	2,0%	0	0,0%	1	2,0%	100,0%	20	7	50
Competitive grants to publicly fund research	30	57,7%	22	42,3%	0	0,0%	0	0,0%	0	0,0%	100,0%	20	5	52
Interconnection between research projects on different neglected diseases	27	52,9%	21	41,2%	2	3,9%	0	0,0%	1	2,0%	100,0%	20	6	51
Raising the scientific profile of neglected disease research (better career/publication opportunities)	27	51,9%	22	42,3%	2	3,8%	0	0,0%	1	1,9%	100,0%	20	5	52
Interdisciplinary research cooperation with e.g. veterinary medicine, traditional medicine, epidemiology	26	51,0%	21	41,2%	3	5,9%	0	0,0%	1	2,0%	100,0%	20	6	51

Table 8-13 continued

Feasibility of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	
	definitely feasible		**possibly feasible**		**possibly unfeasible**		**definitely unfeasible**		**no judgment**			**abandoned**	**missing**	Valid N
International / transcontinental research cooperation involving researchers from developing countries	26	50,0%	23	44,2%	2	3,8%	0	0,0%	1	1,9%	100,0%	20	5	52
Neglected disease R&D as priority in relevant European Union funding programs (e.g. FP7)	26	50,0%	19	36,5%	6	11,5%	0	0,0%	1	1,9%	100%	20	5	52
Building research, technical and regulatory capacity in developing countries	24	46,2%	25	48,1%	2	3,8%	0	0,0%	1	1,9%	100%	20	5	52
Simplified / fast-track funding procedures	21	40,4%	24	46,2%	4	7,7%	0	0,0%	3	5,8%	100%	20	5	52
Government support and funds for multilateral efforts (e.g. WHO-TDR)	21	39,6%	29	54,7%	1	1,9%	1	1,9%	1	1,9%	100%	20	4	53
Protocol and regulatory advice / assistance to neglected disease R&D projects	18	35,3%	27	52,9%	2	3,9%	0	0,0%	4	7,8%	100%	20	6	51
Tax credits / tax incentives)	18	35,3%	19	37,3%	3	5,9%	1	2,0%	10	19,6%	100%	20	6	51
Establishment of accountability systems for funds received	18	34,6%	26	50,0%	5	9,6%	0	0,0%	3	5,8%	100%	20	5	52
Sharing or transfer of technology to developing countries	18	34,0%	26	49,1%	5	9,4%	1	1,9%	3	5,7%	100%	20	4	53

Table 8-13 continued

Feasibility of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	
	definitely feasible		**possibly feasible**		**possibly unfeasible**		**definitely unfeasible**		**no judgment**			**abandoned**	**missing**	Valid N
Link between neglected disease R&D and research and clinical care for priority diseases such as HIV, TB or Malaria	17	32,1%	31	58,5%	3	5,7%	1	1,9%	1	1,9%	100%	20	4	53
Establishment of public (or affordable) preclinical research facilities	16	31,4%	25	49,0%	5	9,8%	0	0,0%	5	9,8%	100%	20	6	51
Private donations to ^real^ pharmaceutical companies to develop drugs for neglected diseases	16	31,4%	17	33,3%	8	15,7%	2	3,9%	8	15,7%	100%	20	6	51
Prize funds with prizes awarded based on degree of innovation	16	30,8%	25	48,1%	6	11,5%	1	1,9%	4	7,7%	100%	20	5	52
Establishment of an international health-needs driven R&D agenda matched to technological opportunities	14	27,5%	27	52,9%	5	9,8%	1	2,0%	4	7,8%	100%	20	6	51
Building innovation clusters for low-profit oriented R&D in developing countries	14	26,9%	30	57,7%	3	5,8%	1	1,9%	4	7,7%	100%	20	5	52
Incentives for the private sector (e.g. advance market commitments, governmental incentives)	14	26,9%	30	57,7%	4	7,7%	1	1,9%	3	5,8%	100%	20	5	52

Table 8-13 continued

Feasibility of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	
	definitely feasible		**possibly feasible**		**possibly unfeasible**		**definitely unfeasible**		**no judgment**			**abandoned**	**missing**	Valid N
Exclusive funds for R&D / budgetary set-asides exclusively for purchasing medicines for neglected diseases	13	25,5%	20	39,2%	12	23,5%	1	2,0%	5	9,8%	100%	20	6	51
Global funders forum to set priorities	13	25,0%	26	50,0%	6	11,5%	3	5,8%	4	7,7%	100%	20	5	52
Parallel measures to improve access to health care and medicines	12	23,5%	30	58,8%	4	7,8%	0	0,0%	5	9,8%	100%	20	6	51
Existing patent regulations (e.g. WTO-TRIPS, Doha-Declaration)	12	23,1%	17	32,7%	7	13,5%	0	0,0%	16	30,8%	100%	20	5	52
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	12	23,1%	26	50,0%	6	11,5%	0	0,0%	8	15,4%	100%	20	5	52
Association of biotechnology to health systems for better delivery of goods	10	19,6%	29	56,9%	4	7,8%	0	0,0%	8	15,7%	100%	20	6	51
Open source regulations (e.g. for scientific data or compound / molecule libraries)	9	17,3%	29	55,8%	10	19,2%	2	3,8%	2	3,8%	100%	20	5	52
Development to phase III trials by public laboratories	8	15,4%	34	65,4%	5	9,6%	2	3,8%	3	5,8%	100%	20	5	52
Separation of innovation incentives from drug prices	8	15,1%	22	41,5%	6	11,3%	5	9,4%	12	22,6%	100%	20	4	53
Market exclusivity	7	13,7%	14	27,5%	14	27,5%	1	2,0%	15	29,4%	100%	20	6	51

Table 8-13 continued

Feasibility of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	
	definitely feasible		**possibly feasible**		**possibly unfeasible**		**definitely unfeasible**		**no judgment**			**abandoned**	**missing**	Valid N
Selective investment (as incentive) in companies which invest in neglected disease R&D	7	13,5%	24	46,2%	15	28,8%	0	0,0%	6	11,5%	100%	20	5	52
Patent pools / more flexible patent laws to improve access to research tools	7	13,2%	20	37,7%	14	26,4%	3	5,7%	9	17,0%	100%	20	4	53
Reorganize intellectual property rights as intellectual monopoly privileges	6	11,8%	13	25,5%	17	33,3%	6	11,8%	9	17,6%	100%	20	6	51
Royalty arrangements for the benefit of neglected disease R&D if private sector receives exclusive license on government-owned invention for any disease	6	11,8%	22	43,1%	11	21,6%	1	2,0%	11	21,6%	100%	20	6	51
New alternative juridical instruments which allow governments to foster essential health research and development	6	11,5%	29	55,8%	9	17,3%	1	1,9%	7	13,5%	100%	20	5	52
Obligation for national governments to invest into neglected disease R&D	6	11,3%	23	43,4%	19	35,8%	2	3,8%	3	5,7%	100%	20	4	53
Exemption of drugs from market exclusivity	5	9,6%	18	34,6%	14	26,9%	5	9,6%	10	19,2%	100%	20	5	52

Table 8-13 continued

Feasibility of Measures (Round II) N= 77														
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid Row N%	Count	Count	
	definitely feasible		**possibly feasible**		**possibly unfeasible**		**definitely unfeasible**		**no judgment**			**abandoned**	**missing**	Valid N
Requirement for developing countries to include research with an adequate budget in all health programs	5	9,6%	19	36,5%	20	38,5%	6	11,5%	2	3,8%	100%	20	5	52
Obligation for the private sector to invest x % of profit made from other drugs/treatments into neglected diseases	5	9,4%	11	20,8%	24	45,3%	9	17,0%	4	7,5%	100%	20	4	53
Price increases (10-20%) for brandname drugs paid by public health programs to invest this profit in neglected diseases	4	7,8%	9	17,6%	22	43,1%	10	19,6%	6	11,8%	100%	20	6	51
International regulations regarding the private sector	4	7,7%	23	44,2%	16	30,8%	5	9,6%	4	7,7%	100%	20	5	52
Voucher systems in developed markets (as with the FDA) for other products	4	7,7%	20	38,5%	7	13,5%	1	1,9%	20	38,5%	100%	20	5	52
Lower private sector influence on R&D priority setting	2	3,8%	19	36,5%	18	34,6%	3	5,8%	10	19,2%	100%	20	5	52
Treaty on cost-effectiveness of new health technologies linked to a competitive tender system	2	3,8%	25	48,1%	6	11,5%	5	9,6%	14	26,9%	100%	20	5	52
Abolish patents	1	1,9%	6	11,5%	21	40,4%	19	36,5%	5	9,6%	100%	20	5	52

Table 8-14 Desirability of measures-Statistics-Round I

Desirability of Measures to promote R&D into neglected diseases-Statistics Round I					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Advance market commitments	97	62	2,0	2,0	0,8
Exemption of drugs from market exclusivity	82	77	2,0	2,0	0,9
Existing patent regulations	89	70	2,7	3,0	1,0
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	98	61	1,7	2,0	0,6
Investment obligations into neglected diseases for drug producers/sellers	100	59	2,1	2,0	0,9
Market exclusivity	85	74	2,8	3,0	1,0
Obligations for national governments to invest into neglected disease R&D	111	48	1,6	1,0	0,7
Open source regulations (e.g. for scientific data / compound libraries)	110	49	1,6	2,0	0,7
Patent pools	76	83	1,9	2,0	0,8
Philanthropic spending	101	58	1,7	2,0	0,6
Prize funds for drug innovation	106	53	1,8	2,0	0,8
Protocol assistance	86	73	1,7	2,0	0,6
Public-private partnerships	107	52	1,6	1,0	0,7
Separation of innovation incentives from drug prices	90	69	1,7	1,5	0,8
Tax credits	80	79	1,9	2,0	0,6
Tiered/differential pricing	80	79	2,0	2,0	0,8

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

Table 8-15 Feasibility of measures-Statistics-Round I

Feasibility of Measures to promote R&D into neglected diseases-Statistics-Round I					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Advance market commitments	87	72	2,0	2,0	0,6
Exemption of drugs from market exclusivity	72	87	2,2	2,0	0,7
Existing patent regulations	78	81	2,2	2,0	0,7
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	91	68	1,8	2,0	0,6
Investment obligations into neglected diseases for drug producers/sellers	95	64	2,4	2,0	0,9
Market exclusivity	68	91	2,3	2,0	0,8
Obligations for national governments to invest into neglected disease R&D	105	54	2,0	2,0	0,9
Open source regulations (e.g. for scientific data / compound libraries)	99	60	1,8	2,0	0,7
Patent pools	68	91	2,0	2,0	0,8
Philanthropic spending	96	63	1,5	1,5	0,6
Protocol assistance	87	72	1,6	2,0	0,5
Prize funds for drug innovation	95	64	1,8	2,0	0,6
Public-private partnerships	100	59	1,5	1,5	0,6
Separation of innovation incentives from drug prices	78	81	2,2	2,0	0,8
Tax credits	76	83	1,8	2,0	0,7
Tiered/differential pricing	69	90	1,9	2,0	0,6

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

Table 8-16 Desirability of measures-Statistics-Round II

Desirability of measures to promote R&D into neglected diseases-Statistics-Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Abolish patents	49	28	2,4	2,0	0,9
Association of biotechnology to health systems for better delivery of goods	46	31	1,9	2,0	0,7
Building innovation clusters for low-profit oriented R&D in developing countries	52	25	1,6	2,0	0,5
Building research, technical and regulatory capacity in developing countries	56	21	1,4	1,0	0,5
Competitive grants to publicly fund research	57	20	1,6	2,0	0,5
Contribution by foreign donors towards capacity building and strengthening the research infrastructure in developing countries	53	24	1,5	1,0	0,6
Development to phase III trials by public laboratories	52	25	1,8	2,0	0,6
Educate / inform the public about the individual and societal burden of disease of neglected diseases	56	21	1,7	2,0	0,7
Establishment of accountability systems for funds received	50	27	1,7	2,0	0,6
Establishment of an international health-needs driven R&D agenda matched to technological opportunities	55	22	1,5	1,0	0,6
Establishment of public (or affordable) preclinical research facilities	55	22	1,7	2,0	0,5
Exclusive funds for R&D / budgetary set-asides exclusively for purchasing medicines for neglected diseases	45	32	1,7	2,0	0,7
Exemption of drugs from market exclusivity	49	28	1,8	2,0	0,9
Existing patent regulations (e.g. WTO-TRIPS, Doha-Declaration)	43	34	2,3	2,0	1,0
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	52	25	1,8	2,0	0,6
Global funders forum to set priorities	49	28	2,1	2,0	0,9
Government support and funds for multilateral efforts (e.g. WHO-TDR)	55	22	1,5	1,0	0,6
Incentives for the private sector (e.g. advance market commitments, governmental incentives)	54	23	1,8	2,0	0,8
Include neglected diseases in university curricula	57	20	1,6	2,0	0,6
Interconnection between research projects on different neglected diseases	56	21	1,7	2,0	0,5
Interdisciplinary research cooperation with e.g. veterinary medicine, traditional medicine, epidemiology	55	22	1,6	2,0	0,5

Table 8-16 continued

Desirability of measures to promote R&D into neglected diseases-Statistics-Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
International / transcontinental research cooperation involving researchers from developing countries	56	21	1,4	1,0	0,5
International regulations regarding the private sector	53	24	1,9	2,0	0,7
Link between neglected disease R&D and research and clinical care for priority diseases such as HIV, TB or Malaria	52	25	1,6	2,0	0,6
Lower private sector influence on R&D priority setting	51	26	2,1	2,0	1,0
Market exclusivity	45	32	2,9	3,0	0,8
Neglected disease R&D as priority in relevant European Union funding programs (e.g. FP7)	57	20	1,4	1,0	0,5
New alternative juridical instruments which allow governments to foster essential health research and development	48	29	1,8	2,0	0,8
Obligation for national governments to invest into neglected disease R&D	53	24	1,8	2,0	0,8
Obligation for the private sector to invest x % of profit made from other drugs/treatments into neglected diseases	50	27	2,0	2,0	1,0
Open source regulations (e.g. for scientific data or compound / molecule libraries)	54	23	1,6	1,0	0,8
Parallel measures to improve access to health care and medicines	54	23	1,4	1,0	0,5
Patent pools / more flexible patent laws to improve access to research tools	47	30	1,7	2,0	0,8
Price increases (10-20%) for brandname drugs paid by public health programs to invest this profit in neglected diseases	44	33	3,0	3,0	0,7
Private donations to ^real^ pharmaceutical companies to develop drugs for neglected diseases	47	30	2,4	2,0	0,9
Prize funds with prizes awarded based on degree of innovation	48	29	1,8	2,0	0,8
Protocol and regulatory advice / assistance to neglected disease R&D projects	52	25	1,7	2,0	0,6
Public-private partnerships	53	24	1,7	1,0	0,9
Raise awareness among policy makers for the impact of neglected diseases on development	55	22	1,5	1,0	0,7
Raising the scientific profile of neglected disease research (better career/publication opportunities)	54	23	1,6	1,5	0,6
Reorganize intellectual property rights as intellectual monopoly privileges	38	39	2,6	2,5	1,1

Table 8-16 continued

Desirability of measures to promote R&D into neglected diseases-Statistics-Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Requirement for developing countries to include research with an adequate budget in all health programs	49	28	2,1	2,0	0,7
Royalty arrangements for the benefit of neglected disease R&D if private sector receives exclusive license on government-owned invention for any disease	41	36	2,2	2,0	1,0
Selective investment (as incentive) in companies which invest in neglected disease R&D	47	30	2,1	2,0	0,8
Separation of innovation incentives from drug prices	46	31	1,8	2,0	0,9
Sharing or transfer of technology to developing countries	52	25	1,5	1,0	0,6
Simplified / fast-track funding procedures	52	25	1,6	1,5	0,7
Tax credits / tax incentives	44	33	2,0	2,0	0,8
Treaty on cost-effectiveness of new health technologies linked to a competitive tender system	36	41	2,2	2,0	0,9
Voucher systems in developed markets (as with the FDA) for other products	37	40	2,3	2,0	0,9

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

Table 8-17 Feasibility of measures-Statistics-Round II

Feasibility of measures to promote R&D into neglected diseases-Statistics-Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Abolish patents	52	25	8,4	8,0	0,9
Association of biotechnology to health systems for better delivery of goods	51	26	7,4	7,0	1,3
Building innovation clusters for low-profit oriented R&D in developing countries	52	25	7,1	7,0	1,1
Building research, technical and regulatory capacity in developing countries	52	25	6,6	7,0	0,7
Competitive grants to publicly fund research	52	25	6,4	6,0	0,5
Contribution by foreign donors towards capacity building and strengthening the research infrastructure in developing countries	50	27	6,5	6,0	0,7
Development to phase III trials by public laboratories	52	25	7,2	7,0	1,0
Educate / inform the public about the individual and societal burden of disease of neglected diseases	52	25	6,5	6,0	0,9
Establishment of accountability systems for funds received	52	25	6,9	7,0	1,0
Establishment of an international health-needs driven R&D agenda matched to technological opportunities	51	26	7,1	7,0	1,1
Establishment of public (or affordable) preclinical research facilities	51	26	7,1	7,0	1,1
Exclusive funds for R&D / budgetary set-asides exclusively for purchasing medicines for neglected diseases	51	26	7,3	7,0	1,2
Exemption of drugs from market exclusivity	52	25	7,9	8,0	1,3
Existing patent regulations (e.g. WTO-TRIPS, Doha-Declaration)	52	25	7,8	7,0	1,6
Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	52	25	7,3	7,0	1,3
Global funders forum to set priorities	52	25	7,2	7,0	1,1
Government support and funds for multilateral efforts (e.g. WHO-TDR)	53	24	6,7	7,0	0,8
Incentives for the private sector (e.g. advance market commitments, governmental incentives)	52	25	7,0	7,0	1,0
Include neglected diseases in university curricula	52	25	6,4	6,0	0,7
Interconnection between research projects on different neglected diseases	51	26	6,6	6,0	0,8
Interdisciplinary research cooperation with e.g. veterinary medicine, traditional medicine, epidemiology	51	26	6,6	6,0	0,8

Table 8-17 continued

Feasibility of measures to promote R&D into neglected diseases-Statistics-Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
International / transcontinental research cooperation involving researchers from developing countries	52	25	6,6	6,5	0,7
International regulations regarding the private sector	52	25	7,7	7,0	1,0
Link between neglected disease R&D and research and clinical care for priority diseases such as HIV, TB or Malaria	53	24	6,8	7,0	0,8
Lower private sector influence on R&D priority setting	52	25	8,0	8,0	1,2
Market exclusivity	51	26	8,1	8,0	1,4
Neglected disease R&D as priority in relevant European Union funding programs (e.g. FP7)	52	25	6,7	6,5	0,8
New alternative juridical instruments which allow governments to foster essential health research and development	52	25	7,5	7,0	1,2
Obligation for national governments to invest into neglected disease R&D	53	24	7,5	7,0	1,0
Obligation for the private sector to invest x % of profit made from other drugs/treatments into neglected diseases	53	24	7,9	8,0	1,0
Open source regulations (e.g. for scientific data or compound / molecule libraries)	52	25	7,2	7,0	0,9
Parallel measures to improve access to health care and medicines	51	26	7,1	7,0	1,1
Patent pools / more flexible patent laws to improve access to research tools	53	24	7,8	7,0	1,3
Price increases (10-20%) for brandname drugs paid by public health programs to invest this profit in neglected diseases	51	26	8,1	8,0	1,1
Private donations to ^real^ pharmaceutical companies to develop drugs for neglected diseases	51	26	7,4	7,0	1,4
Prize funds with prizes awarded based on degree of innovation	52	25	7,1	7,0	1,1
Protocol and regulatory advice / assistance to neglected disease R&D projects	51	26	6,9	7,0	1,1
Public-private partnerships	53	24	6,5	6,0	0,9
Raise awareness among policy makers for the impact of neglected diseases on development	52	25	6,4	6,0	0,7
Raising the scientific profile of neglected disease research (better career/publication opportunities)	52	25	6,6	6,0	0,8
Reorganize intellectual property rights as intellectual monopoly privileges	51	26	8,0	8,0	1,3

Table 8-17 continued

Feasibility of measures to promote R&D into neglected diseases-Statistics-Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Requirement for developing countries to include research with an adequate budget in all health programs	52	25	7,6	8,0	1,0
Royalty arrangements for the benefit of neglected disease R&D if private sector receives exclusive license on government-owned invention for any disease	51	26	7,8	7,0	1,3
Selective investment (as incentive) in companies which invest in neglected disease R&D	52	25	7,5	7,0	1,1
Separation of innovation incentives from drug prices	53	24	7,8	7,0	1,4
Sharing or transfer of technology to developing countries	53	24	7,0	7,0	1,0
Simplified / fast-track funding procedures	52	25	6,8	7,0	1,0
Tax credits / tax incentives	51	26	7,3	7,0	1,5
Treaty on cost-effectiveness of new health technologies linked to a competitive tender system	52	25	8,1	7,0	1,4
Voucher systems in developed markets (as with the FDA) for other products	52	25	8,3	8,0	1,5

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

IV. Desirability and feasibility of a regulatory instrument

Table 8-18 Desirability of a regulatory instrument-Round I

Desirability of a regulatory instrument-Round I				
		Frequency	Percent	Valid Percent
Valid	very desirable	50	31,4	44,2
	desirable	50	31,4	44,2
	undesirable	8	5,0	7,1
	very undesirable	2	1,3	1,8
	no judgment	3	1,9	2,7
	Total	113	71,1	100,0
Missing	abandoned	39	24,5	
	missing	7	4,4	
	Total	46	28,9	
Total		159	100,0	

Table 8-19 Feasibility of a regulatory instrument-Round I

Feasibility of a regulatory instrument-Round I				
		Frequency	Percent	Valid Percent
Valid	very feasible	16	10,1	14,2
	feasible	72	45,3	63,7
	unfeasible	9	5,7	8,0
	very unfeasible	4	2,5	3,5
	no judgment	12	7,5	10,6
	Total	113	71,1	100,0
Missing	abandoned	39	24,5	
	missing	7	4,4	
	Total	46	28,9	
Total		159	100,0	

Table 8-20 Desirability and feasibility of a regulatory instrument-Statistics-Round I

Desirability and feasibility of a regulatory instrument-Statistics-Round I					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Desirability of a regulatory instrument	110	49	1,7	2,0	0,7
Feasibility of a regulatory instrument	101	58	2,0	2,0	0,6

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

Table 8-21 Desirability and feasibility of a regulatory instrument-Statistics-Round II

Desirability and feasibility of a regulatory instrument-Statistics Round II					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Desirability of a regulatory instrument	50	27	1,6	1,0	0,8
Feasibility of a regulatory instrument	53	24	2,1	2,0	0,8

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

Table 8-22 Desirability of a Regulatory Instrument * Place of Residence-Round I

Desirability of a Regulatory Instrument * Place of Residence – Round I						
			Place of Residence			Total
			Developed country	Developing country	Threshold country / emerging market	
Desirability of a regulatory instrument	very desirable	Count	35	11	3	49
		% within Place of Residence	42,2%	52,4%	42,9%	44,1%
		% of Total	31,5%	9,9%	2,7%	44,1%
	desirable	Count	36	10	4	50
		% within Place of Residence	43,4%	47,6%	57,1%	45,0%
		% of Total	32,4%	9,0%	3,6%	45,0%
	undesirable	Count	8	0	0	8
		% within Place of Residence	9,6%	0,0%	0,0%	7,2%
		% of Total	7,2%	0,0%	0,0%	7,2%
	very undesirable	Count	2	0	0	2
		% within Place of Residence	2,4%	0,0%	0,0%	1,8%
		% of Total	1,8%	0,0%	0,0%	1,8%
	no judgment	Count	2	0	0	2
		% within Place of Residence	2,4%	0,0%	0,0%	1,8%
		% of Total	1,8%	0,0%	0,0%	1,8%
Total		Count	83	21	7	111
		% within Place of Residence	100,0%	100,0%	100,0%	100,0%
		% of Total	74,8%	18,9%	6,3%	100,0%

Table 8-23 Feasibility of a regulatory instrument * Place of Residence-Round I

Feasibility of a Regulatory Instrument * Place of Residence - Round I						
			Place of Residence			Total
			Developed country	Developing country	Threshold country / emerging market	
Feasibility of a regulatory instrument	very feasible	Count	8	7	1	16
		% within Place of Residence	9,6%	33,3%	14,3%	14,4%
		% of Total	7,2%	6,3%	,9%	14,4%
	feasible	Count	55	13	4	72
		% within Place of Residence	66,3%	61,9%	57,1%	64,9%
		% of Total	49,5%	11,7%	3,6%	64,9%
	unfeasible	Count	8	0	1	9
		% within Place of Residence	9,6%	0,0%	14,3%	8,1%
		% of Total	7,2%	0,0%	,9%	8,1%
	very unfeasible	Count	3	0	0	3
		% within Place of Residence	3,6%	0,0%	0,0%	2,7%
		% of Total	2,7%	0,0%	0,0%	2,7%
	no judgment	Count	9	1	1	11
		% within Place of Residence	10,8%	4,8%	14,3%	9,9%
		% of Total	8,1%	,9%	,9%	9,9%
Total		Count	83	21	7	111
		% within Place of Residence	100,0%	100,0%	100,0%	100,0%
		% of Total	74,8%	18,9%	6,3%	100,0%

Table 8-24 Desirability of a Regulatory Instrument * Place of Residence-Round II

Desirability of a Regulatory Instrument * Place of Residence – Round II						
			Place of Residence			Total
			Developed country	Developing country	Threshold country/emerging market	
Desirability of a regulatory instrument	very desirable	Count	17	6	2	25
		% within Place of Residence	43,6%	54,5%	100,0%	48,1%
		% of Total	32,7%	11,5%	3,8%	48,1%
	desirable	Count	15	5	0	20
		% within Place of Residence	38,5%	45,5%	0,0%	38,5%
		% of Total	28,8%	9,6%	0,0%	38,5%
	undesirable	Count	2	0	0	2
		% within Place of Residence	5,1%	0,0%	0,0%	3,8%
		% of Total	3,8%	0,0%	0,0%	3,8%
	very undesirable	Count	2	0	0	2
		% within Place of Residence	5,1%	0,0%	0,0%	3,8%
		% of Total	3,8%	0,0%	0,0%	3,8%
	no judgment	Count	3	0	0	3
		% within Place of Residence	7,7%	0,0%	0,0%	5,8%
		% of Total	5,8%	0,0%	0,0%	5,8%
Total		Count	39	11	2	52
		% within Place of Residence	100,0%	100,0%	100,0%	100,0%
		% of Total	75,0%	21,2%	3,8%	100,0%

Table 8-25 Feasibility of a Regulatory Instrument * Place of Residence-Round II

Feasibility of a Regulatory Instrument * Place of Residence – Round II						
			Place of Residence			Total
			Developed country	Developing country	Threshold country / emerging market	
Feasibility of a regulatory instrument	definitely feasible	Count	5	3	1	9
		% within Place of Residence	12,8%	27,3%	50,0%	17,3%
		% of Total	9,6%	5,8%	1,9%	17,3%
	possibly feasible	Count	25	6	1	32
		% within Place of Residence	64,1%	54,5%	50,0%	61,5%
		% of Total	48,1%	11,5%	1,9%	61,5%
	possibly unfeasible	Count	6	2	0	8
		% within Place of Residence	15,4%	18,2%	0,0%	15,4%
		% of Total	11,5%	3,8%	0,0%	15,4%
	definitely unfeasible	Count	3	0	0	3
		% within Place of Residence	7,7%	0,0%	0,0%	5,8%
		% of Total	5,8%	0,0%	0,0%	5,8%
Total		Count	39	11	2	52
		% within Place of Residence	100,0%	100,0%	100,0%	100,0%
		% of Total	75,0%	21,2%	3,8%	100,0%

Table 8-26 Desirability of a Regulatory Instrument*Professional Affiliation-Round I

Desirability of a regulatory instrument * Professional affiliation - Round one, six subgroups							
		Academia	**National government/ parliament**	**Industry**	**International organization**	**Non-governmental organization**	**Other**
very desirable	Count	28	2	1	2	8	9
	% within Affiliation	46,7%	33,3%	8,3%	40,0%	50,0%	69,2%
	% of Total	25,0%	1,8%	0,9%	1,8%	7,1%	8,0%
desirable	Count	26	4	6	3	7	4
	% within Affiliation	43,3%	66,7%	50,0%	60,0%	43,8%	30,8%
	% of Total	23,2%	3,6%	5,4%	2,7%	6,3%	3,6%
undesirable	Count	4	0	4	0	0	0
	% within Affiliation	6,7%	0,0%	33,3%	0,0%	0,0%	0,0%
	% of Total	3,6%	0,0%	3,6%	0,0%	0,0%	0,0%
very undesirable	Count	0	0	1	0	1	0
	% within Affiliation	0,0%	0,0%	8,3%	0,0%	6,3%	0,0%
	% of Total	0,0%	0,0%	0,9%	0,0%	0,9%	0,0%
no judgment	Count	2	0	0	0	0	0
	% within Affiliation	3,3%	0,0%	0,0%	0,0%	0,0%	0,0%
	% of Total	1,8%	0,0%	0,0%	0,0%	0,0%	0,0%
Total	Count	60	6	12	5	16	13
	% within Affiliation	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
	% of Total	53,6%	5,4%	10,7%	4,5%	14,3%	11,6%

Table 8-27 Feasibility of a Regulatory Instrument*Professional Affiliation-Round I

Feasibility of a regulatory instrument * Professional affiliation - Round one, six subgroups							
		Academia	**National government / parliament**	**Industry**	**International organization**	**Non-governmental organization**	**Other**
very feasible	Count	12	0	1	0	1	2
	% within Affiliation	20,0%	0,0%	8,3%	0,0%	6,3%	15,4%
	% of Total	10,7%	0,0%	0,9%	0,0%	0,9%	1,8%
feasible	Count	36	5	5	4	13	9
	% within Affiliation	60,0%	83,3%	41,7%	80,0%	81,3%	69,2%
	% of Total	32,1%	4,5%	4,5%	3,6%	11,6%	8,0%
unfeasible	Count	5	1	3	0	0	0
	% within Affiliation	8,3%	16,7%	25,0%	0,0%	0,0%	0,0%
	% of Total	4,5%	0,9%	2,7%	0,0%	0,0%	0,0%
very unfeasible	Count	1	0	2	0	1	0
	% within Affiliation	1,7%	0,0%	16,7%	0,0%	6,3%	0,0%
	% of Total	0,9%	0,0%	1,8%	0,0%	0,9%	0,0%
no judgment	Count	6	0	1	1	1	2
	% within Affiliation	10,0%	0,0%	8,3%	20,0%	6,3%	15,4%
	% of Total	5,4%	0,0%	0,9%	0,9%	0,9%	1,8%
Total	Count	60	6	12	5	16	13
	% within Affiliation	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
	% of Total	53,6%	5,4%	10,7%	4,5%	14,3%	11,6%

Table 8-28 Desirability of a Regulatory Instrument*Professional Affiliation-Round II

Desirability of a regulatory instrument * Professional affiliation - Round two, seven subgroups								
		Academia	**National government / parliament**	**Industry**	**International organization**	**Non-governmental organization**	**Public Private Partnership**	**Other**
very desirable	Count	16	3	1	0	5	0	1
	% within Affiliation	57,1%	75,0%	16,7%	0,0%	83,3%	0,0%	50,0%
	% of Total	30,8%	5,8%	1,9%	0,0%	9,6%	0,0%	1,9%
desirable	Count	11	1	3	1	1	1	1
	% within Affiliation	39,3%	25,0%	50,0%	25,0%	16,7%	50,0%	50,0%
	% of Total	21,2%	1,9%	5,8%	1,9%	1,9%	1,9%	1,9%
undesirable	Count	0	0	0	1	0	1	0
	% within Affiliation	0,0%	0,0%	0,0%	25,0%	0,0%	50,0%	0,0%
	% of Total	0,0%	0,0%	0,0%	1,9%	0,0%	1,9%	0,0%
very undesirable	Count	0	0	2	0	0	0	0
	% within Affiliation	0,0%	0,0%	33,3%	0,0%	0,0%	0,0%	0,0%
	% of Total	0,0%	0,0%	3,8%	0,0%	0,0%	0,0%	0,0%
no judgment	Count	1	0	0	2	0	0	0
	% within Affiliation	3,6%	0,0%	0,0%	50,0%	0,0%	0,0%	0,0%
	% of Total	1,9%	0,0%	0,0%	3,8%	0,0%	0,0%	0,0%
Total	Count	28	4	6	4	6	2	2
	% within Affiliation	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
	% of Total	53,8%	7,7%	11,5%	7,7%	11,5%	3,8%	3,8%

Table 8-29 Feasibility of a Regulatory Instrument*Professional Affiliation -Round II

Feasibility of a regulatory instrument * Professional affiliation - Round two, seven subgroups								
		Academia	**National government / parliament**	**Industry**	**International organization**	**Non-governmental organization**	**Public Private Partnership**	**Other**
definitely feasible	Count	7	1	0	0	2	0	0
	% within Affiliation	25,0%	25,0%	0,0%	0,0%	33,3%	0,0%	0,0%
	% of Total	13,5%	1,9%	0,0%	0,0%	3,8%	0,0%	0,0%
possibly feasible	Count	17	3	4	1	3	2	1
	% within Affiliation	60,7%	75,0%	66,7%	25,0%	50,0%	100,0%	50,0%
	% of Total	32,7%	5,8%	7,7%	1,9%	5,8%	3,8%	1,9%
possibly unfeasible	Count	3	0	0	3	1	0	1
	% within Affiliation	10,7%	0,0%	0,0%	75,0%	16,7%	0,0%	50,0%
	% of Total	5,8%	0,0%	0,0%	5,8%	1,9%	0,0%	1,9%
definitely unfeasible	Count	1	0	2	0	0	0	0
	% within Affiliation	3,6%	0,0%	33,3%	0,0%	0,0%	0,0%	0,0%
	% of Total	1,9%	0,0%	3,8%	0,0%	0,0%	0,0%	0,0%
Total	Count	28	4	6	4	6	2	2
	% within Affiliation	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
	% of Total	53,8%	7,7%	11,5%	7,7%	11,5%	3,8%	3,8%

V. Criteria for a definition of neglected diseases

Table 8-30 Criteria for a definition of neglected diseases-Round II

Criteria for a definition of neglected diseases													
	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Count	Valid Row N%	Total Valid N	Missing	Total
		most important		**important**		**unimportant**		**least important**		**no judgment**			
Disease severity: life-threatening, serious, debilitating, chronic	12	20,3%	36	61,0%	6	10,2%	3	5,1%	2	3,4%	59	18	77
Lack of awareness / visibility of relevant diseases	16	27,6%	28	48,3%	7	12,1%	5	8,6%	2	3,4%	58	19	77
Economic situation of affected population	18	30,5%	31	52,5%	5	8,5%	3	5,1%	2	3,4%	59	18	77
Prevalence, burden of disease	20	33,9%	27	45,8%	8	13,6%	2	3,4%	2	3,4%	59	18	77
Lack of access to existing effective treatment	21	35,0%	31	51,7%	4	6,7%	3	5,0%	1	1,7%	60	17	77
Absence of effective treatment and lack of ongoing research	27	45,8%	28	47,5%	2	3,4%	1	1,7%	1	1,7%	59	18	77

Table 8-31 Criteria for a definition of neglected diseases-Statistics-Round II

Criteria for a definition of neglected diseases					
	N		Mean	Median	Std. Deviation
	Valid	Missing*			
Absence of effective treatment and lack of ongoing research	58	19	1,6	2,0	0,6
Lack of awareness / visibility of relevant diseases	56	21	2,0	2,0	0,9
Disease severity: life-threatening, serious, debilitating, chronic	57	20	2,0	2,0	0,7
Economic situation of affected population	57	20	1,9	2,0	0,8
Lack of access to existing effective treatment	59	18	1,8	2,0	0,8
Prevalence, burden of disease	57	20	1,9	2,0	0,8

* Includes participants who abandoned the questionnaire prior to this question, who did not answer the question and who answered “no judgment”

9 Annex II – Survey Documentation

Reference Manager 11.0 / Literature Search

	Keywords in document title or keyword list	Boolean operator	Keywords in document title or keyword list	Boolean operator	Keywords in document title or keyword list	Boolean operator	Keywords in document title or keyword list	Boolean operator	Keywords in document title or keyword list	Boolean operator
Search-Strategy	neglected disease*		orphan disease*	OR	orphan disease*	OR	neglected disease*	AND	Medical Research and Development Treaty	
							treaty			
			rare disease*		rare disease	AND				
					neglected disease*					

* A wildcard (*) was added to retrieve the words “disease” as well as “diseases”.

Mailvorlagen verwalten

Vorlagenliste

Vorlage erstellen

Login:
Angela Fehr
Users Online:
28 user(s) online
104 respondent(s) online
Date (GMT):
27.02.2008 16:33:34
Local date (+0:00):
27.02.2008 16:33:34

Mailvorschau

Absender: Angela Fehr <Delphi_Survey@gmx.net>

Betreff: Research Project "Neglected and Orphan Diseases"

Mailtext:

Dear Professor #u_name#,

As part of a research project on neglected and orphan diseases, the University of Bielefeld (Germany) School of Public Health conducts a two-round Delphi survey to gather experts' opinions on possible solutions for the existing deficits in neglected disease R&D, with a special focus on mechanisms contained in orphan drug regulations and in the draft Medical Research and Development Treaty. With this Email, we are kindly requesting your participation in the survey.

The questionnaire for the first round of survey opens when you click on the following link: #code_complete#. The questionnaire will take about 10 minutes to complete. In the first round of survey, you are asked to rank items and to suggest additional items to the questionnaire. In the second round (which will open shortly after the closing of the first round), you will see frequency distributions from the first round and possible new items based on the suggestions from the first round. All replies, comments and suggestions to the questionnaire are collected anonymously from the respondents; the respondents' identities will at no time be visible to other survey participants.

Attached to this mail is a pdf-document with a short summary of the aims and methods of this survey. We are contacting about 400 international experts from different academic backgrounds (medicine, economics, law, political science, public health) and professional affiliations (academia, industry, internatinal organizations, national governments/parliaments, non-governmental organizations) to participate in this survey.

The assessment by experts and stakeholders of current R&D-stimulating measures and their possible suggestions for additional measures is of crucial importance for this research project. We would therefore be very grateful if you shared your opinion and participated in the survey.

Thank you very much for your time and support!

Sincerely,

Prof. Dr. Oliver Razum, MD, MSc
Prof. Dr. Petra Thürmann, MD
(Project Chairs)

Angela Fehr, M.A. (USA)
(Research Coordinator)

Anhänge: Project Summary final.pdf

Delphi Survey on Neglected and Orphan Diseases

Project Summary

Research questions:	1) Which incentives are effective in stimulating research and development on neglected and orphan diseases? 2) Is it meaningful and/or necessary to have a regulatory instrument to frame the incentives for neglected diseases?
Research design:	Delphi survey in two rounds
Survey participants:	Experts and stakeholders in the fields of neglected diseases and rare/orphan diseases
Project location:	Dept. of Epidemiology & International Health, School of Public Health, University of Bielefeld (Germany)
Project chairs:	Professor Dr. Oliver Razum, MD, MSc Professor Dr. Petra Thürmann, MD
Research coordinator:	Angela Fehr, M.A. (USA) University of Bielefeld (Germany)

Project background / institutional affiliation

This survey is part of a research project on neglected and orphan diseases, which is conducted at the Department of Epidemiology & International Public Health at the School of Public Health, University of Bielefeld, Germany. The project is supervised by the Department Head, Prof. Dr. Oliver Razum, MD, MSc, and by Prof. Dr. Petra Thürmann, MD, Chair of Clinical Pharmacology, University of Witten/Herdecke, Philipp Klee-Institute for Clinical Pharmacology, HELIOS Klinikum Wuppertal.

Research questions

Neglected diseases and rare, or “orphan” diseases, have in common that they offer little financial incentive for investing in research and drug development (R&D). Orphan drug regulations such as the U.S. Orphan Drug Act of 1983 or the European Union’s Regulation on orphan medicinal products, enforced in 2000, were developed to stimulate orphan drug development and to ameliorate the situation for patients with

rare diseases. For neglected diseases, no such regulations exist yet. One option under discussion is to apply incentives similar to those contained in orphan drug laws to stimulate neglected disease R&D. A different approach was taken in 2005, when the draft for a Medical Research and Development Treaty (MRDT) was submitted to the World Health Organization (WHO), designed to "create a new global framework for supporting medical research and development."

With this research project, we are asking experts and stakeholders to share their opinion on the necessity of a regulatory instrument to stimulate neglected disease R&D, and on the measures such regulation would have to include.

Method

The method chosen for this research is a ***Delphi survey.*** Delphi surveys are anonymous surveys among a heterogeneous group of experts who represent various perspectives to an issue under research. Owing to rankings and priority-settings, the method and its outcomes are credible and operational for policy-makers.

In this survey, you are asked to give priority judgment on causes for the problem of neglected diseases, as well as on possible solutions. The questionnaire we have developed covers a number of causes as well as measures included in the U.S. and the European regulations on orphan drugs [1]. Additionally, we have listed approaches from the draft Medical Research and Development Treaty [2].

Delphi surveys are conducted in several rounds. ***This survey has two rounds***. In the first round, you are asked to rank the items given in the questionnaire, and, if you wish, complement them with your own suggestions. The questionnaire for the second round (in which only first-round participants can participate), will include these additions made by participants. Also in the second round questionnaire, you will see frequency distributions of the answers given in the first round. If you wish, you may change your priority judgment based on these results.

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[1] http://www.fda.gov/orphan/oda.htm;
http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=32000R0141&model=guichett

[2] http://www.cptech.org/workingdrafts/rndtreaty4.pdf).

Final frequency distributions from the second round will be mailed to you after the survey has been closed and evaluated.

Technical Procedure

The Email you received contains the link to the questionnaire for the first round. Participants in a pre-test needed around ***10 minutes to complete*** the questionnaire. The first round can be accessed for two weeks starting today.

Participants

We are contacting about 400 experts and stakeholders worldwide from the field of neglected and rare diseases, who took part in international conferences on the issues of neglected and rare diseases and/or are authors of relevant scientific publications on the topic. Their professional affiliations are in academia, industry, international organizations, national governments/parliaments or non-governmental organizations.

The survey is anonymous. Participants' identities will not at any time during the analysis and publication of data, be visible to other survey participants or correlated with individual survey results.

Goal

The goal of this survey is to learn which R&D-stimulating measures are given preference by the participating experts and stakeholders.

We are very grateful for your support of this research project. Please do not hesitate to contact us if you have any questions about this survey.

On behalf of the project team,
Sincerely,
Angela Fehr, Research Coordinator

Email: Delphi_Survey@gmx.net

9%

Welcome and thank you for supporting this research project on neglected and orphan diseases.

This is the first of two rounds of the project's Delphi survey. The survey will take about 10 minutes to complete.

The first round can be accessed until March 29, 2008.

Next

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I. Neglected Diseases

Neglected diseases are disease states where there are inadequate, ineffective or no means to prevent, treat, diagnose or cure them. (WHO/CIPIH)

1. What, in your opinion, are the most important causes for this deficit?

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	most important	important	unimportant	least important	no judgement
a) No or inadequate direct public funding for research and developement (R&D) for neglected diseases	○	○	○	○	○
b) No or inadequate private sector investment into R&D for neglected diseases	○	○	○	○	○
c) No or inadequate incentives for the private sector to invest into R&D for neglected diseases	○	○	○	○	○
d) No or insufficient sustainability of public funding for R&D for neglected diseases	○	○	○	○	○
e) No or ineffective drugs for neglected diseases	○	○	○	○	○
f) No or inadequate access to effective drugs for neglected diseases	○	○	○	○	○
g) No or inadequate research infrastructure in countries with neglected diseases	○	○	○	○	○

2. Are there items you would like to add to this list?

h)

i)

j)

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II. Orphan diseases

For several years, laws or regulations have existed to foster research and development (R&D) for orphan diseases. These diseases are characterized by a very low prevalence which led to deficits in R&D. Orphan drug laws were developed to provide R&D incentives.

1. Are you familiar with orphan drug laws?

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

- Yes, I have active knowledge of the provisions in these laws (e.g. through application processes for orphan drug status)
- Yes, I have passive knowledge of orphan drug laws (e.g. through publications)
- No, I have no knowledge about the provisions contained in orphan drug laws

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27%

2. How effective do you consider orphan drug laws?

Technical advice: Please use your left mouse button to make your choice. You may change your answer by clicking another button.

very effective	effective	ineffective	very ineffective	no judgement
○	○	○	○	○

3. How effective are the individual provisions of orphan drug laws?

Technical advice: Please use your left mouse button to make your choice. You may change your answer by clicking another button.

	very effective	effective	ineffective	very ineffective	no judgement
a) Fee reduction / Fee waivers	○	○	○	○	○
b) Market exclusivity	○	○	○	○	○
c) Protocol assistance	○	○	○	○	○
d) Tax credits	○	○	○	○	○

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36%

III. New options for neglected diseases?

1. Following is a list of measures to promote medical research and development.

a) How desirable* is it to implement these measures to foster R&D for neglected diseases?
**Please see definition at the bottom of this page.*

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	very desirable	desirable	undesirable	very undesirable	no judgement
i) Advance market commitments	○	○	○	○	○
ii) Exemption of drugs from market exclusivity	○	○	○	○	○
iii) Existing patent regulations	○	○	○	○	○
vi) Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	○	○	○	○	○
v) Investment obligations into neglected diseases for drug producers/sellers	○	○	○	○	○
vi) Market exclusivity	○	○	○	○	○
vii) Obligations for national governments to invest into neglected disease R&D	○	○	○	○	○
viii) Open source regulations (e.g. for scientific data / compound libraries)	○	○	○	○	○
ix) Patent pools	○	○	○	○	○
x) Philantrophic spending	○	○	○	○	○
xi) Prize funds for drug innovation	○	○	○	○	○
xii) Protocol assistance	○	○	○	○	○
xiii) Public-private partnerships	○	○	○	○	○
xiv) Separation of innovation incentives from drug prices	○	○	○	○	○
xv) Tax credits	○	○	○	○	○
xvi) Tiered/differential pricing	○	○	○	○	○

Definition "Desirability"

Very desirable:

extremely beneficial / will have a positive effect and little to no negative effect

Desirable:
beneficial / will have a positive effect and little to no negative effect

Undesirable:
harmful / will have a negative effect

Very undesirable:
extremely harmful / will have a major negative effect

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[45%]

b) How feasible* is it to implement these measures to foster R&D for neglected diseases?
**Please see definition at the bottom of this page.*

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	very feasible	feasible	unfeasible	very unfeasible	no judgment
i) Advance market commitments	○	○	○	○	○
ii) Exemption of drugs from market exclusivity	○	○	○	○	○
iii) Existing patent regulations	○	○	○	○	○
iv) Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	○	○	○	○	○
v) Investment obligations into neglected diseases for drug producers/sellers	○	○	○	○	○
vi) Market exclusivity	○	○	○	○	○
vii) Obligations for national governments to invest into neglected disease R&D	○	○	○	○	○
viii) Open source regulations (e.g. for scientific data / compound libraries)	○	○	○	○	○
ix) Patent pools	○	○	○	○	○
x) Philantrophic spending	○	○	○	○	○
xi) Protocol assistance	○	○	○	○	○
xii) Prize funds for drug innovation	○	○	○	○	○
xiii) Public-private partnerships	○	○	○	○	○
xiv) Separation of innovation incentives from drug prices	○	○	○	○	○
xv) Tax credits	○	○	○	○	○
xvi) Tiered/differential pricing	○	○	○	○	○

Definition "Feasibility"

Definitely feasible:
no hindrance to implementation / no political roadblocks / acceptable to the public

Possibly feasible:
some indication this is implementable / minor political roadblocks / further consideration or preparation to be given to public reaction

Possible unfeasible:
some indication this is unworkable / severe political resistances / difficult to communicate to the public

Definitely unfeasible:
all indications are negative / politically unworkable / cannot be implemented

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55%

2. What other measures not yet in force could promote R&D for neglected diseases? Please list the three most important measures.

a)

b)

c)

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64%

3. Do you consider it desirable to have a regulatory instrument (a law, regulation or treaty) to foster R&D for neglected diseases?

Technical advice: Please use your left mouse button to make your choice. You may change your answer by clicking another button.

very desirable	desirable	undesirable	very undesirable	no judgement
○	○	○	○	○

Would you like to comment on your position on this question?
Please fill in the text field.

4. Do you consider it feasible to implement such a regulatory instrument?

Technical advice: Please use your left mouse button to make your choice. You may change your answer by clicking another button.

very feasible	feasible	unfeasible	very unfeasible	no judgment
○	○	○	○	○

Would you like to comment on your position on this question?

Please fill in the text field.

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73%

5. Under orphan drug laws, a disease has to meet specific criteria of prevalence and disease severity (e.g. life-threatening, seriously debilitating, serious and chronic condition) to be classified as are rare, or orphan disease.

Which are the criteria a disease would have to meet to be classified as "neglected disease" under a regulatory instrument?

Please name the three most important criteria.

Please fill in the text fields.

1

2

3

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82%

IV. Conclusion

1. Do you have any comments on this Delphi survey or on the questionnaire?

2. You have completed the questionnaire. In conclusion, we would be grateful if you gave us the following demographic information.

a) What is your professional background?

Technical advice: Please use your left mouse button to check boxes.
You may check more than one box. You may change your answer by clicking another button.

- ☐ Economy
- ☐ Law
- ☐ Medicine
- ☐ Political Science
- ☐ Public Health
- ☐ Other

b) What is your current professional affiliation?

Technical advice: Please use your left mouse button to check boxes. You may change your answer by clicking another button.

- ○ Academia
- ○ National government/parliament
- ○ Industry
- ○ International organization
- ○ Non-governmental organization
- ○ Other

c) Your place of residence is in a

Technical advice: Please use your left mouse button to check boxes. You may change you answer by clicking another radio-button.

- Developed country
- Developing country
- Threshold country/emerging market

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100%

Thank you for participating in this Delphi survey!

This was the first of two rounds. We will now evaluate the outcome of this round.

All participants who completed the first round will shortly receive an email containing the link to the questionnaire for the second (and last) round of this survey.

In the second round, you will see the results of this first round as well as comments and suggestions which the participating experts have added to this questionnaire.

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Mailvorlagen verwalten

Vorlagenliste

Vorlage erstellen

Login:
Angela Fehr

Users Online:
15 user(s) online
30 respondent(s) online

Date (GMT):
24.03.2008 19:33:01

Local date (+0:00):
24.03.2008 19:33:01

Mailvorschau

Absender: Angela Fehr <Delphi_Survey@gmx.net>

Betreff: Research Project "Neglected and Orphan Diseases"

Mailtext:

Dear Professor / Dr. #u_name#,

Thank you very much for filling out the questionnaire for the Delphi survey on neglected and orphan diseases. The survey software indicates to us that your questionnaire has not been filled out completely. We would therefore like to ask whether you wish to complete the questionnaire. Your personal code to resume participation in the survey (#code_complete#) will be active until March 29, 2008. The answers you have given to date have been saved; however, you may revise them when you re-enter your questionnaire.

Thank you very much for your time and support!

Sincerely,
pp.

Angela Fehr
Research Coordinator

EFS Survey

Status | Projekte | Mitarbeiter | Optionen

English Help Logout

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Mailvorlagen verwalten

Vorlagenliste

Vorlage erstellen

Login:
Angela Fehr
Users Online:
5 user(s) online
21 respondent(s) online
Date (GMT):
24.03.2008 19:49:46
Local date (+0:00):
24.03.2008 19:49:46

Mailvorschau

Absender: Angela Fehr <Delphi_Survey@gmx.net>

Betreff: Research Project "Neglected and Orphan Diseases"

Mailtext:

Dear Professor#u_name#,

With this Email we would like to renew our request and kindly ask whether you would be willing to participate in a two-round Delphi survey on neglected and orphan diseases. The survey is part of a research project conducted at the University of Bielefeld (Germany) School of Public Health; its objective is to gather experts' opinions on possible solutions for the existing deficits in neglected disease R&D, with a special focus on mechanisms contained in orphan drug regulations and in the draft Medical Research and Development Treaty.

The questionnaire will take about 10 minutes to complete. The following link is your personal access code to the survey:

#code_complete#.

The link will be active until March 29, 2008, when we will close the first round, evaluate the results and open the second (and last) round. A request to participate in the second round will then be sent to all first-round participants.

We would be very grateful if you contributed your expertise to the survey!

Thank you very much for your time and support.

Sincerely,

Prof. Dr. Oliver Razum, MD, MSc
Prof. Dr. Petra Thürmann, MD
(Project Chairs)

Angela Fehr, M.A. (USA)
(Research Coordinator)

Mailvorlagen verwalten

Vorlagenliste

Vorlage erstellen

Login:
Angela Fehr
Users Online:
8 user(s) online
77 respondent(s) online
Date (GMT):
10.07.2008 19:02:45
Local date (+0:00):
10.07.2008 19:02:45

Mailvorschau

Absender: Angela Fehr <Delphi_Survey@gmx.net>

Betreff: Research Project "Neglected and Orphan Diseases"

Mailtext:

Dear Professor / Dr. #u_name#,

You were so kind to participate in the first round of a Delphi survey which the University of Bielefeld (Germany) School of Public Health conducts as part of a research project on neglected and orphan diseases. The aim of this project is to gather experts' opinions on possible solutions for the existing deficits in neglected disease R&D.

117 experts participated in the first round of survey. We have received many comments and suggestions, and we are very grateful that today we can present you with a much more differentiated list of options to rank and choose from.

The principle of a Delphi survey is to share the revised version of the questionnaire with the same panel of experts and ask them for their opinion again.

The questionnaire for the second round of survey opens when you click on the following link: #code_complete#. It contains new and modified items, frequency distributions from the first round as well as participants' comments on specific items and on the survey as such.

We would be very grateful if you shared your opinion and participated in the second round of this survey. We sincerely hope that our research project can make a contribution to the ongoing international debate, both in terms of its outcome and of its methodological approach, on the global issue of neglected diseases.

Thank you very much for your time and support!

Sincerely,

Prof. Dr. Oliver Razum, MD, MSc
Prof. Dr. Petra Thürmann, MD
(Project Chairs)

Angela Fehr, M.A. (USA)
(Research Coordinator)

10%

Welcome and thank you for supporting this research project on neglected and orphan diseases.

This is the second of two rounds of the project's Delphi survey.
The survey will take about 15-20 minutes to complete. The questionnaire can be accessed until August 6, 2008.

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Introduction to the second round

We would like to sincerely thank all participants of the first survey for the time and effort they took to contribute to this research project. We have received many suggestions for additional items and for revising existing items of the questionnaire. The questionnaire for the second round has been expanded and modified accordingly.

We have also received a considerable number of explanatory comments, which we have included as pdf-documents in the questionnaire; you can open the documents by clicking on a link on the corresponding page.

To show the first round's frequency distributions, each page of this modified questionnaire contains tabulations. A click on a blue questionmark on each page opens a pop-up-window to display the graphs.

Before starting the questionnaire, would you like to read participants' comments on the survey from the first round? Please click on the following link to open the pdf-document which contains the comments. comments_on_the_survey.pdf

The questionnaire starts on the following page. Thank you again for contributing your expertise to this survey!

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I. Neglected Diseases

Neglected diseases are disease states where there are inadequate, ineffective or no means to prevent, treat, diagnose or cure them. (WHO/CIPIH)

What, in your opinion, are the most important causes for this deficit? Please rate the items below. *The list has been modified and expanded following participants' suggestions in the first round.*

To see the frequency distributions from the first round, please click on the blue questionmark.

Here you find the suggestions made by participants in the first round: causes_for_r_d_deficit.pdf

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	most important	important	unimportant	least important	no judgement
1) Disease-specific research difficulties (unknown etiology, lack of research material)	○	○	○	○	○
2) Inadequate research priorities in private sector R&D	○	○	○	○	○
3) Lack of awareness /visibility of neglected diseases	○	○	○	○	○
4) Lack of health-needs driven priority setting in public funding	○	○	○	○	○
5) No or inadequate access to effective drugs for neglected diseases	○	○	○	○	○
6) No or inadequate health delivery infrastructure and staff in developing countries	○	○	○	○	○
7) No or inadequate incentives for the private sector to invest into R&D for neglected diseases	○	○	○	○	○
8) No or inadequate private sector investment into R&D for neglected diseases	○	○	○	○	○
9) No or inadequate research coordination	○	○	○	○	○
10) No or inadequate research infrastructure in countries with neglected diseases	○	○	○	○	○

	most important	important	unimportant	least important	no judgement
11) No or ineffective drugs for neglected diseases	○	○	○	○	○

12) No or insufficient direct public funding for research and development (R&D) for neglected diseases	○	○	○	○	○
13) No or insufficient sustainability of public funding for R&D for neglected diseases	○	○	○	○	○
14) Poverty as disease-proliferating factor (i.a. inadequate prevention, inadequate housing, lack of clean water) in endemic countries	○	○	○	○	○
15) Poverty as reason for market failure (perception of no market for drugs, insufficient R&D)	○	○	○	○	○

Would you like to add a comment?
Please fill in the text field.

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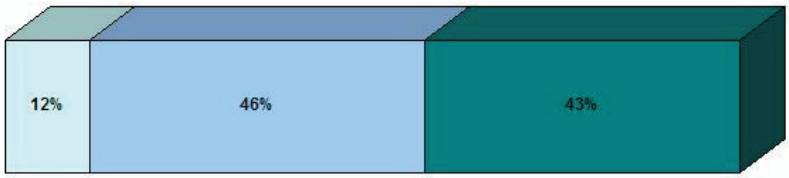
[40%]

II. Orphan diseases

In the first round of the survey we asked the participants whether they were familiar with orphan drug laws and, if they were, to judge the laws' performance. Following are the frequency distributions for these questions.

II. 1. For several years, laws or regulations have existed to foster research and development (R&D) for orphan diseases. These diseases are characterized by a very low prevalence which led to deficits in R&D.
Are you familiar with orphan drug laws?

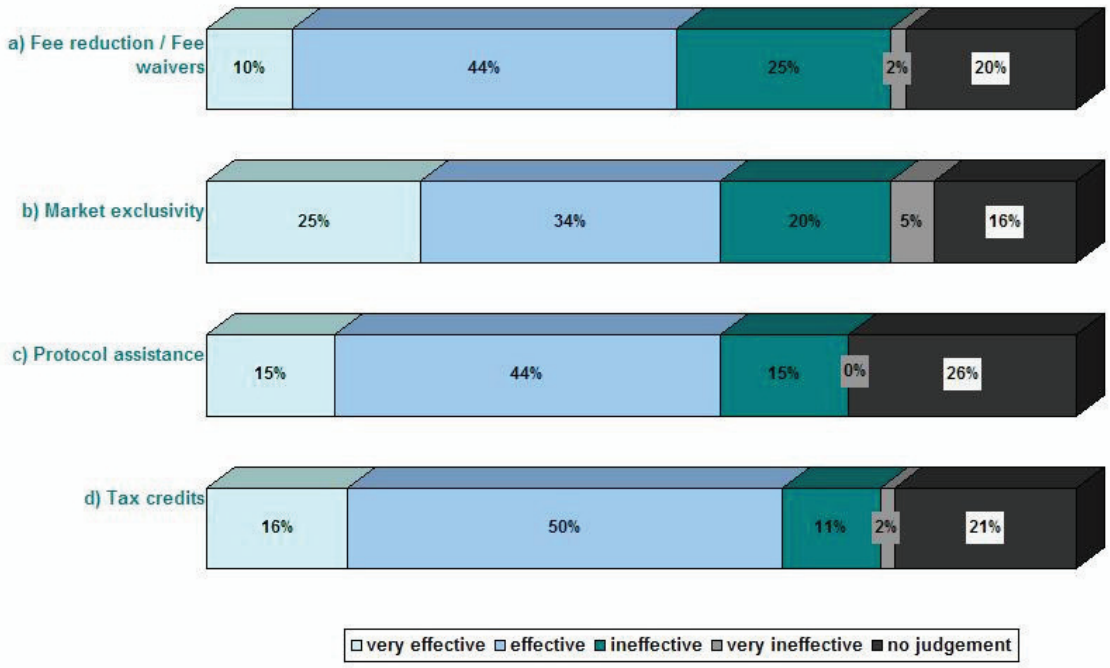


- Yes, I have active knowledge of the provisions in these laws (e.g. through application processes for orphan drug status)
- Yes, I have passive knowledge of orphan drug laws (e.g. through publications)
- No, I have no knowledge about the provisions contained in orphan drug laws

II. 2. How do you rate the effectiveness of orphan drug laws?
(only participants who answered "yes" to the previous question II. 1.)

Very effective Effective Ineffective Very ineffective No judgement

II. 3. How effective are the individual provisions of orphan drug laws?
(only participants who answered "yes" to the previous question II. 1.)



Would you like to comment on these outcomes?
Please fill in the text field.

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III. Orphan drug laws contain definitions of what constitutes an orphan disease. In the first round of survey, we asked participants to suggest criteria which could make up a definition of "neglected diseases".

We have subsumed these suggestions into the categories below.

Please indicate how important you consider each item for a definition of neglected diseases.
Here you find the complete list of suggestions:criteria_for_nd_definition.pdf

Please click on the button of your choice. You may de-select your choice by clicking another button.

	most important	important	unimportant	least important	no judgement
1) Absence of effective treatment and lack of ongoing research	○	○	○	○	○
2) Lack of awareness / visibility of relevant diseases	○	○	○	○	○
3) Disease severity: life-threatening, serious, debilitating, chronic	○	○	○	○	○
4) Economic situation of affected population	○	○	○	○	○
5) Lack of access to existing effective treatment	○	○	○	○	○
6) Prevalence, burden of disease	○	○	○	○	○

Would you like to add a comment?
Please fill in the text field.

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60%

***Definition "Desirability"**

Very desirable:
extremely beneficial / will have a positive effect and little to no negative effect

Desirable:
beneficial / will have a positive effect and little to no negative effect

Undesirable:
harmful / will have a negative effect

Very undesirable:
extremely harmful / will have a major negative effect

IV. New options for neglected diseases?

Following is a list of measures to promote medical research and development.

a) How desirable* are these measures to foster R&D for neglected diseases? *The list has been modified and expanded following participants' suggestions in the first round.*

To see the frequency distributions from the first round, please click on the blue questionmark.

Here you find the suggestions made by participants in the first round:
measures_to_promote_r_d_for_neglected_diseases.pdf

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	very desirable	desirable	undesirable	very undesirable	no judgement
1) Abolish patents	○	○	○	○	○
2) Association of biotechnology to health systems for better delivery of goods	○	○	○	○	○
3) Building innovation clusters for low-profit oriented R&D in developing countries	○	○	○	○	○
4) Building research, technical and regulatory capacity in developing countries	○	○	○	○	○
5) Competitive grants to publicly fund research	○	○	○	○	○
6) Contribution by foreign donors towards capacity building and strenthening the research infrastructure in developing countries	○	○	○	○	○
7) Development to phase III trials by public laboratories	○	○	○	○	○

8) Educate / inform the public about the individual and societal burden of disease of neglected diseases	○	○	○	○	○
9) Establishment of accountability systems for funds received	○	○	○	○	○
10) Establishment of an international health-needs driven R&D agenda matched to technological opportunities	○	○	○	○	○

	very desirable	desirable	undesirable	very undesirable	no judgement
11) Establishment of public (or affordable) preclinical research facilities	○	○	○	○	○
12) Exclusive funds for R&D / budgetary set-asides exclusively for purchasing medicinces for neglected diseases	○	○	○	○	○
13) Exemption of drugs from market exclusivity	○	○	○	○	○
14) Existing patent regulations (e.g. WTO-TRIPS, Doha-Declaration)	○	○	○	○	○
15) Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	○	○	○	○	○
16) Global funders forum to set priorities	○	○	○	○	○
17) Government support and funds for multilateral efforts (e.g. WHO-TDR)	○	○	○	○	○
18) Incentives for the private sector (e.g. advance market commitments, governmental incentives)	○	○	○	○	○
19) Include neglected diseases in university curricula	○	○	○	○	○
20) Interconnection between research projects on different neglected diseases	○	○	○	○	○

	very desirable	desirable	undesirable	very undesirable	no judgement
21) Interdisciplinary research cooperation with e.g. veterinary medicine, traditional medicine, epidemiology	○	○	○	○	○

22) International / transcontinental research cooperation involving researchers from developing countries	○	○	○	○	○
23) International regulations regarding the private sector	○	○	○	○	○
24) Link between neglected disease R&D and research and clinical care for priority diseases such as HIV, TB or Malaria	○	○	○	○	○
25) Lower private sector influence on R&D priority setting	○	○	○	○	○
26) Market exclusivity	○	○	○	○	○
27) Neglected disease R&D as priority in relevant European Union funding programs (e.g. FP7)	○	○	○	○	○
28) New alternative juridical instruments which allow governments to foster essential health research and development	○	○	○	○	○
29) Obligation for national governments to invest into neglected disease R&D	○	○	○	○	○
30) Obligation for the private sector to invest x % of profit made from other drugs/treatments into neglected diseases	○	○	○	○	○

	very desirable	**desirable**	**undesirable**	**very undesirable**	**no judgement**
31) Open source regulations (e.g. for scientific data or compound / molecule libraries)	○	○	○	○	○
32) Parallel measures to improve access to health care and medicines	○	○	○	○	○
33) Patent pools / more flexible patent laws to improve access to research tools	○	○	○	○	○
34) Price increases (10-20%) for brandname drugs paid by public health programs to invest this profit in neglected disease R&D	○	○	○	○	○
35) Private donations to "real" pharmaceutical companies to develop drugs for neglected	○	○	○	○	○

diseases

36) Prize funds with prizes awarded based on degree of innovation	○	○	○	○	○
37) Protocol and regulatory advice / assistance to neglected disease R&D projects	○	○	○	○	○
38) Public-private partnerships	○	○	○	○	○
39) Raise awareness among policy makers for the impact of neglected diseases on development	○	○	○	○	○
40) Raising the scientific profile of neglected disease research (better career/publication opportunities)	○	○	○	○	○

	very desirable	**desirable**	**undesirable**	**very undesirable**	**no judgement**
41) Reorganize intellectual property rights as intellectual monopoly privileges	○	○	○	○	○
42) Requirement for developing countries to include research with an adequate budget in all health programs	○	○	○	○	○
43) Royalty arrangements for the benefit of neglected disease R&D if private sector receives exclusive license on government-owned invention for any disease	○	○	○	○	○
44) Selective investment (as incentive) in companies which invest in neglected disease R&D	○	○	○	○	○
45) Separation of innovation incentives from drug prices	○	○	○	○	○
46) Sharing or transfer of technology to developing countries	○	○	○	○	○
47) Simplified / fast-track funding procedures	○	○	○	○	○
48) Tax credits / tax incentives	○	○	○	○	○
49) Treaty on cost-effectiveness of new health technologies linked to a competitive tender system	○	○	○	○	○

50) Voucher systems in developed markets (as with the FDA) for other products	○	○	○	○	○

Would you like to add a comment?
Please fill in the text field.

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70%

Definition "Feasibility"

Definitely feasible:
no hindrance to implementation / no political roadblocks / acceptable to the public

Possibly feasible:
some indication this is implementable / minor political roadblocks / further consideration or preparation to be given to public reaction

Possibly unfeasible:
some indication this is unworkable / severe political resistances / difficult to communicate to the public

Definitely unfeasible:
all indications are negative / politically unworkable / cannot be implemented

b) According to your experiences and judgement, how feasible* is it to implement these measures to foster R&D for neglected diseases?

Technical advice: Please use your left mouse button to click the button of your choice. You may change your answer by clicking another button.

	definitely feasible	possibly feasible	possibly unfeasible	definitely unfeasible	no judgement
1) Abolish patents	○	○	○	○	○
2) Association of biotechnology to health systems for better delivery of goods	○	○	○	○	○
3) Building innovation clusters for low-profit oriented R&D in developing countries	○	○	○	○	○
4) Building research, technical and regulatory capacity in developing countries	○	○	○	○	○
5) Competitive grants to publicly fund research	○	○	○	○	○
6) Contribution by foreign donors towards capacity building and strenthening the research infrastructure in developing countries	○	○	○	○	○
7) Development to phase III trials by public laboratories	○	○	○	○	○
8) Educate / inform the public about the individual and societal burden of disease of neglected diseases	○	○	○	○	○

9) Establishment of accountability systems for funds received	○	○	○	○	○
10) Establishment of an international health-needs driven R&D agenda matched to technological opportunities	○	○	○	○	○
	definitely feasible	**possibly feasible**	**possibly unfeasible**	**definitely unfeasible**	**no judgement**
11) Establishment of public (or affordable) preclinical research facilities	○	○	○	○	○
12) Exclusive funds for R&D / budgetary set-asides exclusively for purchasing medicinces for neglected diseases	○	○	○	○	○
13) Exemption of drugs from market exclusivity	○	○	○	○	○
14) Existing patent regulations (e.g. WTO-TRIPS, Doha-Declaration)	○	○	○	○	○
15) Fee reduction / Fee waivers (e.g. for marketing approval, scientific advice)	○	○	○	○	○
16) Global funders forum to set priorities	○	○	○	○	○
17) Government support and funds for multilateral efforts (e.g. WHO-TDR)	○	○	○	○	○
18) Incentives for the private sector (e.g. advance market commitments, governmental incentives)	○	○	○	○	○
19) Include neglected diseases in university curricula	○	○	○	○	○
20) Interconnection between research projects on different neglected diseases	○	○	○	○	○
	definitely feasible	**possibly feasible**	**possibly unfeasible**	**definitely unfeasible**	**no judgement**
21) Interdisciplinary research cooperation with e.g. veterinary medicine, traditional medicine, epidemiology	○	○	○	○	○
22) International / transcontinental research cooperation involving researchers from developing countries	○	○	○	○	○
23) International regulations regarding the private sector	○	○	○	○	○

24) Link between neglected disease R&D and research and clinical care for priority diseases such as HIV, TB or Malaria	○	○	○	○	○
25) Lower private sector influence on R&D priority setting	○	○	○	○	○
26) Market exclusivity	○	○	○	○	○
27) Neglected disease R&D as priority in relevant European Union funding programs (e.g. FP7)	○	○	○	○	○
28) New alternative juridical instruments which allow governments to foster essential health research and development	○	○	○	○	○
29) Obligation for national governments to invest into neglected disease R&D	○	○	○	○	○
30) Obligation for the private sector to invest x % of profit made from other drugs/treatments into neglected diseases	○	○	○	○	○

	definitely feasible	**possibly feasible**	**possibly unfeasible**	**definitely unfeasible**	**no judgement**
31) Open source regulations (e.g. for scientific data or compound / molecule libraries)	○	○	○	○	○
32) Parallel measures to improve access to health care and medicines	○	○	○	○	○
33) Patent pools / more flexible patent laws to improve access to research tools	○	○	○	○	○
34) Price increases (10-20%) for brandname drugs paid by public health programs to invest this profit in neglected disease R&D	○	○	○	○	○
35) Private donations to "real" pharmaceutical companies to develop drugs for neglected diseases	○	○	○	○	○
36) Prize funds with prizes awarded based on degree of innovation	○	○	○	○	○

37) Protocol and regulatory advice / assistance to neglected disease R&D projects	○	○	○	○	○
38) Public-private partnerships	○	○	○	○	○
39) Raise awareness among policy makers for the impact of neglected diseases on development	○	○	○	○	○
40) Raising the scientific profile of neglected disease research (better career/publication opportunities)	○	○	○	○	○

	definitely feasible	**possibly feasible**	**possibly unfeasible**	**definitely unfeasible**	**no judgement**
41) Reorganize intellectual property rights as intellectual monopoly privileges	○	○	○	○	○
42) Requirement for developing countries to include research with an adequate budget in all health programs	○	○	○	○	○
43) Royalty arrangements for the benefit of neglected disease R&D if private sector receives exclusive license on government-owned invention for any disease	○	○	○	○	○
44) Selective investment (as incentive) in companies which invest in neglected disease R&D	○	○	○	○	○
45) Separation of innovation incentives from drug prices	○	○	○	○	○
46) Sharing or transfer of technology to developing countries	○	○	○	○	○
47) Simplified / fast-track funding procedures	○	○	○	○	○
48) Tax credits / tax incentives	○	○	○	○	○
49) Treaty on cost-effectiveness of new health technologies linked to a competitive tender system	○	○	○	○	○
50) Voucher systems in developed markets (as with the FDA) for other products	○	○	○	○	○

Would you like to add a comment?
Please fill in the text field.

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80%

V. In the first round of this survey, we asked whether participants considered it desirable and feasible to have a regulatory instrument (a law, regulation or treaty) to foster R&D for neglected diseases.
To see the frequency distribution of answers from the first round, please click on the blue questionmark.

Here you find the comments made by survey participants on the desirability of a regulatory instrument: desirability_of_a_regulatory_instrument.pdf and on the feasibility of such an instrument: feasibility_of_a_regulatory_instrument.pdf

a) In the light of the views expressed by the survey participants on this matter, do you consider it desirable to have a regulatory instrument to foster R&D for neglected diseases?

Technical advice: Please use your left mouse button to make your choice. You may de-select your choice by clicking another button.

very desirable	desirable	undesirable	very undesirable	no judgement
○	○	○	○	○

b) In the light of the views expressed by the survey participants on this matter, do you consider it feasible to have a regulatory instrument to foster R&D for neglected diseases?

Technical advice: Please use your left mouse button to make your choice. You may de-select your choice by clicking another button.

definitely feasible	possibly feasible	possibly unfeasible	definitely unfeasible	no judgement
○	○	○	○	○

Would you like to add a comment?
Please fill in the text field.

Back Next

Cancel

90%

VI. You have completed the questionnaire. In conclusion, may we ask you again to give us some demographic information. Collecting this information again will allow us to determine whether the composition of the panel has changed between the first and the second round of survey. Thank you for your support!

a) What is your professional background?
(Please click on the blue questionmark to see the frequency distribution from the first round)

Technical advice: Please use your left mouse button to check boxes.
You may check more than one box.

- ☐ Biology / Biomedical Sciences
- ☐ Economy
- ☐ Law
- ☐ Medicine
- ☐ Pharmaceutical Sciences
- ☐ Political Science
- ☐ Public Health
- ☐ Veterinary medicine
- ☐ Other

b) What is your current professional affiliation?
(Please click on the blue questionmark to see the frequency distribution from the first round)

Technical advice: Please use your left mouse button to check boxes. You may change your answer by clicking another button.

- ○ Academia
- ○ National government/parliament
- ○ Industry
- ○ International organization
- ○ Non-governmental organization
- ○ Public Private Partnership
- ○ Other

c) Your place of residence is in a
(Please click on the blue questionmark to see the frequency distribution from the first round)

Technical advice: Please use your left mouse button to check boxes. You may change you answer

by clicking another radio-button.
(A click on the blue questionmark opens the frequency distribution of the 1st round)

- Developed country
- Developing country
- Threshold country/emerging market

Would you like to add a final comment on this survey?
Please fill in the text field.

Back Next

Cancel

100%

Thank you for participating in this Delphi survey!

This was the last of two rounds. We will now evaluate the outcome of the survey and send you our first results as soon as possible.

Close window

Mailvorschau

Absender: abfberlin@gmx.net

Betreff: Research Project "Neglected and Orphan Diseases" - 2nd Round of Survey

Mailtext:

Dear Professor / Dr. #u_name#,

You were so kind to participate in the first round of a Delphi survey on neglected and orphan diseases in March. This Delphi Survey is designed as a discussion process among experts. So, unlike an opinion survey, it is conducted in several rounds. We are now in the second round, and have put a new questionnaire online. It contains new items which were suggested by the experts in the first round. Additionally, the results of the previous round as well as comments and explanatory notes received by the participants of the first round are made available.

We are contacting you because according to the survey software you have not accessed the questionnaire or have not filled it out completely. We would like to cordially remind you of the upcoming deadline and ask you to participate in the second round (which will also be the last round). To complete the questionnaire, please click on the following link which is your personal access code:

#code_complete#

The questionnaire can be accessed until August 6, 2008. Participants who have already completed the questionnaire needed about 15 minutes to fill it out. Please contact us if you have any questions regarding this survey or technical difficulties in accessing the questionnaire. In case you do not wish to proceed with the questionnaire we would like to sincerely thank you for your contribution to the first round of survey!

Thank you very much for your contribution to this research project conducted at the University of Bielefeld (Germany), School of Public Health!

Sincerely,

Prof. Dr. Oliver Razum, MD, MSc
Prof. Dr. Petra Thürmann, MD
(Project Chairs)

Angela Fehr, M.A. (USA)
(Research Coordinator)

Mailvorschau

Absender: abfberlin@gmx.net

Betreff: Delphi Survey Second Round

Mailtext:

Dear Professor / Dr. #u_name#,

At the request of some participants who were unable to complete the questionnaire until August 6, we extend the time for the survey until Friday, August 15, 2008.

With kind regards,

Angela Fehr
Research Coordinator

Your link to the survey:

#code_complete#

- Mailvorlagen

Mailvorschau

Absender: Angela Fehr <Delphi_Survey@gmx.net>
Betreff: Delphi Survey on Neglected and Orphan Diseases-Results 2nd Round

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Mailtext:

Dear Professor / Dr. #u_name#,

You were so kind to participate in the second round of the Delphi survey which the University of Bielefeld (Germany) School of Public Health conducted as part of a research project on neglected and orphan diseases. The aim of this project was to gather experts' opinions on possible solutions for the existing deficits in neglected disease R&D.

117 experts participated in the first round of survey, of which 56 also completed the questionnaire for the second round. At the request of several experts, the deadline for filling out the questionnaire for the second round was extended twice. Today, we are sending you the frequency distributions of the second and last round of survey, together with the comments we received during this round. Please click on the following link to access the website which contains the results of the second round: #code_complete#

Each round of a Delphi survey consists of the survey itself and of the feedback to the previous round. Our Delphi survey involved two rounds; the survey therefore closes with this feedback.

As the next step in our project, we will perform an in-depth analysis of the data, taking into account the quantitative and qualitative data we have received, but also the advice which you as participating experts have given us regarding the interpretation of the data and the conclusions which may be drawn from them.

Your expert contribution to this survey enabled us to conduct our research project. We sincerely thank you for your time and effort!

With kind regards,

Angela Fehr, M.A. (U.S.A.)
(Research Coordinator)

Prof. Dr. Oliver Razum, MD, MSc
Prof. Dr. Petra Thuermann, MD
(Project Chairs)