Beatrice Stirner

Under the direction of
Professor Daniel Kraus and Professor Olivier Guillod

Research and development of pharmaceutical products for neglected diseases: legal means for stimulation in Switzerland

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Under the direction of

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To those affected by neglected diseases.

And to my parents for their love and support.
(Und meinen Eltern für ihre Liebe und Unterstützung.)

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Foreword

Many diseases touching developing countries are defined as *neglected* because pharmaceutical products that could prevent or treat them are the object of no or insufficient research and development (R&D). Lack of R&D for pharmaceutical products for those diseases, including vaccines and diagnostic kits, is a broadly recognized reality that a country like Switzerland, leader in the pharmaceutical industry, cannot afford to ignore.

The main reason invoked for this lack of interest is the absence of financial stimulation. Indeed, and contrary to diseases that are also found in industrialized countries, diseases prevalent only in developing countries, including in particular in least developed ones, unfortunately represent no commercial interest for the pharmaceutical industry. The latter is no philanthropic one, but works under the same market rules as any business entity. What needs to be done is therefore to find incentives that would compensate this market failure.

Several initiatives, most of them private (although often financed at least partially by public money) or the result of public-private partnerships try to fill in the gap in financing the development of pharmaceutical products to fight such neglected diseases. Treatments are currently under development, some in the phase of clinical tests and others in the phase of admission by marketing authorities. Such initiatives must be encouraged and stimulated in order to become the norm.

Patents constitute one of the instruments leading to innovation in the field of health. Harmonization of international intellectual property law has certainly contributed to stimulate R&D. But the positive effect of these international agreements, as well as of the flexibility reaffirmed and contained in the Declarations and Decisions of the World Trade Organization relatively to public health and access to medicines is not felt in the field of neglected diseases.

Switzerland, host to both an important pharmaceutical industry and a recognized humanitarian tradition, can, and should play an efficient role

in R&D in the field of neglected diseases. Our country indeed benefits from capacities allowing the undertaking of R&D in this field and can hence appear as an important international actor. Switzerland is not insensitive to the needs of developing countries, as shown by its recent revision of Swiss patent law: it is indeed one of the first laws to authorize compulsory licenses for the exportation of pharmaceuticals and to require the declaration of source of genetic resources and traditional knowledge used in a product or process for which a patent is filed. The fact that a former President of the Swiss Confederation chaired the World Health Organization Commission on intellectual property rights, innovation and public health is another strong signal.

Last but not least, the presence in Geneva of the main international organizations and of several public-private partnerships dealing with the issue also calls on our country to play an even more active role in this matter in the future.

The present book is the result of a research project financed by the Swiss National Science Foundation. It proceeds to a welcome systematic analysis of the causes explaining the lack of stimulation for R&D in Switzerland for products which could fight neglected diseases. It makes a number of proposals allowing for a change of paradigm. We strongly hope that it will constitute a useful source of inspiration for the circles that try to encourage R&D into pharmaceutical products against neglected diseases, in Switzerland and elsewhere, contributing thereby in a modest manner to make the expression "neglected diseases" disappear from our vocabulary.

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Neuchâtel, 27 June 2010

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Special thanks go to all my interview partners – representatives from the Swiss government departments, the pharmaceutical industry, the product development partnerships for neglected diseases, the research institutions, the international organization and the non-governmental organizations, who made time to respond to my questions and provided me with valuable information and materials.

My heartfelt gratitude goes to my family and friends for their support and for their prayers during all the time of the research project, and particular the last months of the preparation of this report.

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While I appreciate the contributions and information I received and share credits with all those who supported me in one way or the other, I take personal responsibility for the views expressed in the report.

Summer 2010 Beatrice Stirner

Abbreviations and acronyms

APC	Advanced Purchase Commitment
ARV	Antiretroviral medicament
BMGF	Bill and Melinda Gates Foundation
CIPIH	World Health Organization Commission on Intellectual Property Rights, Innovation and Public Health
CRO	Contract Research Organization
CSR	Corporate Social Responsibility
DFID	United Kingdom Department for International Development
DNDi	Drugs for Neglected Diseases initiative
EDCTP	European and Developing Countries Clinical Trials Partnership
EFTA	European Free Trade Association
EMEA	European Medicines Agency
EPC	European Patent Convention
EPFL	Ecole Polytechnique Fédérale de Lausanne
EPO	European Patent Office
EU	European Union
EUROCORE	European Collaborative Research
FDA	United States Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
FOPH	Swiss Federal Office for Public Health
GAVI	Global Alliance for Vaccines and Immunization
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria

GFHR	Global Forum for Health Research
GSPA	WHO Global Strategy and Plan of Action
ICESCR	International Covenant on Economic, Social and Cultural Rights
HRP	WHO/World Bank Special Programme of Research Development and Research Training in Human Reproduction
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IGWG	World Health Organization Intergovernmental Working Group on Public health, Innovation and Intellectual Property
IIP	Swiss Institute of Intellectual Property
iOWH	Institute for OneWorldHealth
IP	Intellectual Property
IPR	Intellectual Property Right
MDG	Millennium Development Goals
MMV	Medicines for Malaria Venture
MNC	Multinational company
MRDT	International Medicinal R&D Treaty
NGO	Nongovernmental organization
NRP	National Research Program
OECD	Organization for Economic Co-operation and Development
ODA	Official Development Assistance
ODR	Orphan Drug Regulation
PACTT	Technology Transfer Office of the University and the University Hospitals of Lausanne
PDP	Product development partnership

PPP	Public-private partnership
PRV	Priority Review Voucher
SDC	Swiss Agency for Development Cooperation
SER	Swiss State Secretariat for Education and Research
SMC	Small and medium-sized companies
SNF	Swiss National Science Foundation
STI	Swiss Tropical Institute
TDR	UNICEF, UNDP, World Bank and WHO Special Programme for Research and Training in Tropical Diseases
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UDHR	United Nations' Declaration of Human Rights
UN	United Nations
UNCTAD	United Nations Conference on Trade and Development
UNIDO	United Nations Industrial Development Organization
US	United States
VAT	Value added tax
WHA	World Health Assembly
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Study objective

Pharmaceutical products are the most effective technologies to diagnose, prevent, and treat diseases. The majority of illnesses, in particular infectious diseases, may be prevented, alleviated or cured with existing essential medicines, in combination with appropriate public health intervention.

However, a large part of the world's population lacks adequate access to life-saving pharmaceutical products, despite the enormous scientific and industrial progress in the biomedical R&D, and the financial means of the world as a whole to provide access to medicines to all. The issue reflects both, the non-availability to entire societies of effective medical interventions, which are distributed elsewhere, as well as the failure to develop safe, effective, appropriate quality medicines for major diseases affecting predominately or exclusively least developed and developing countries (L)DCs.

The purpose of this research is to investigate the lack of sufficient incentives for the development of new medical products for those diseases that almost exclusively occur in impoverished countries and regions, the so-called neglected diseases.

The first part of the research focuses on the review and evaluation of existing knowledge on the topic. It provides particularly an analysis of international law on public health, intellectual property, including aspects of the World Trade Organizations' (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), the Doha Ministerial Declaration on the TRIPS agreement and public health and related WTO General Council decisions; as well as international human rights law and Resolutions of the World Health Assembly. It further includes the investigation of proposals for improvements to the current patent-based incentive regime for pharmaceutical R&D.

In order to implement practical considerations to the necessity of stimulating R&D of pharmaceutical products for neglected diseases, the second part of the research contains the results of interviews and consulta-

tions with stakeholders that are involved in the pharmaceutical research and development (R&D) for neglected diseases in Switzerland.

As a result the research aims to make proposals allowing the development of policies and actions that could be implemented in Switzerland to stimulate R&D of pharmaceutical products for neglected diseases within the global intellectual property and public health framework.

The study covers sources and developments until autumn 2009.

Executive summary

Industrialized countries and least developed and developing countries ((L)DCs) have committed in various international (legal) frameworks to solve the urgent health problems in resource-poor regions in order to contribute to their socio-economic development and to balance the existing inequality in global health. In directly addressing the health issues prevalent in (L)DCs, the World Health Assembly Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA) calls upon governments of Member States and other relevant stakeholders to develop new thinking on innovation of and access to medicines. Neglected diseases are not within the regular business of the pharmaceutical industry and governments in industrialized countries. In most cases, these countries lack the prevalence of these infections, thus often also the policies and strategies to spur related innovation of pharmaceutical products. As part of their international commitments, industrialized countries have agreed to a more sensitive approach to the health issues in resource-constrained regions. This includes a short- and medium-term commitment to adequately address R&D priorities of (L)DCs in their national health R&D policies. It requires the development and implementation of incentive schemes for health-related innovation, thus the integration of neglected diseases in both (national and international) push and pull programs.

Based on the findings, this study develops the following recommendations for the stimulation of pharmaceutical products for neglected diseases in Switzerland:

1. The support of public-private product development partnerships (PDPs)

The support of PDPs is the principal mechanism to ensure the continuing and increasing R&D of pharmaceutical products for neglected diseases.

a) Financial support

Financial support is the critical point. It requires increased and steady direct funding of the organizations. Funding should be provided in a longer term commitment for several years to ensure the flexibility and credibility of the PDPs.

New sources of funding for innovation in neglected diseases technologies may be considered and promoted. An opportunity to diversify and increase the funding base at the international level could be the extension of the mandate of existing mechanisms such as the Global Fund for AIDS, Malaria and Tuberculosis to neglected diseases, or the establishment of a fund for related R&D. Furthermore, other funding mechanisms focused on private capital markets (such as an International Finance Facility for neglected diseases) might be considered to generate additional finances.

b) The creation of incentives for collaborations with PDPs

PDPs are dependent on the contributions of other stakeholders, particularly from the private sector. Partnering and collaboration could be supported by tax credits for neglected diseases R&D activities; by research grants for public research institutions for research related to neglected diseases; by the implementation of special programs, for example, within the funding structure of the Swiss Innovation Promotion Agency (CTI) to encourage the transitional science collaboration between various stakeholders from the academic and the private sector and PDPs; or by implementing special programs for the support of PDPs within the structure of the Swiss Secretariat for Education and Research (SER).

c) The creation of a network structure within Switzerland to link PDPs to all relevant private and public stakeholders in the biomedical, biotechnological and pharmaceutical sector within the Swiss territory.

d) Facilitating the yearly tax burden of PDPs

This may be achieved by a change of the legal status of PDPs from a Swiss foundation to an international organization in order to enable the PDPs to benefit from the special tax advantages provided to the new status; or by a regulation at the cantonal level in the Canton of Geneva, where many PDPs are situated.

2. Promotion and implementation of push and pull incentives

Push and pull incentives should be implemented to provide flexibilities to interested stakeholders and to encourage a variety of activities of public and private stakeholders involved in the pharmaceutical R&D process in Switzerland.

a) Push incentives

- The consideration of the implementation of **tax incentives** for biomedical and pharmaceutical R&D activities, with particular emphasis on neglected diseases;
- The promotion of **patent pools** for technologies relevant to neglected diseases among public and private sector actors;
- The development and implementation of a federal strategy concerning a **social licensing practice** related to innovations with neglected diseases background, particularly among PRIs, including universities; the promotion of a social licensing practice also among other stakeholders such as pharmaceutical and biotechnology companies;
- The implementation of incentives concerning the **regulatory process**, including the regulation of a scientific advice procedure for neglected diseases product developers; the implementation of a fast track option for neglected diseases products; the waiving of fees related to the approval process.

b) Pull incentives

The promotion of the **advanced purchase commitments** and the **prize fund** models at international level should be considered where appropriate to encourage the pharmaceutical product development for a particular neglected disease. Switzerland should further consider its financial participation in related current and future programs that are implemented at the international level.

3. Support of relevant international organizations

a) UNICEF, UNDP, World Bank and WHO Special Programme for Research and Training in Tropical Diseases (TDR)

The Special Programme for Research and Training in Tropical Diseases (TDR) has been successful for many years in pharmaceutical product development for neglected diseases in partnership with private and public actors. The international organization will continue its activities related to neglected diseases R&D for diseases that are not addressed by PDPs or other organizations. The continuous financial support of TDR will be important for the pharmaceutical product development for diseases of (L)DCs not yet addressed. Projects and activities of the TDR have increased in numbers and funding should consider these additional responsibilities accordingly.

b) World Health Organization (WHO)

The WHO is the health-specialized United Nations body. Neglected diseases are implemented in various programs of the international organization, such as the Essential Medicines Programme, the Prequalification Programme, or various control programs related to neglected diseases. Moreover, after governments, the WHO is the second responsible actor for the implementation of the GSPA. According responsibilities need to be supported financially, and funding contributions should reflect the increased tasks of the organization.

4. The implementation of the WHA Global strategy and plan of action (GSPA)

Switzerland has been pro-active in the processes of the WHO Commission on Intellectual Property, Innovation and Public Health and Intergovernmental Working Group on Public Health, Innovation and of the Intellectual Property that led to the adoption of the GSPA. The country should continue its engagement by implementing the specific actions of the strategy. It should also develop national strategies in the following areas:

- The promotion of knowledge and technology transfer to (L)DCs among all stakeholders, particularly the private sector actors. This may include, for example, the increased support of exchange programs between Swiss and (L)DC universities; the increase of grant programs for (L)DCs PhD candidates and scientists for studies or research in Switzerland; the further promotion of network structures between Swiss and (L)DCs researchers; and the creation of incentives for the private sector to encourage the transfer of knowledge and technology related to pharmaceutical development or other sectors such as biotechnology.
- The support of programs that help improve the clinical trial performance in (L)DCs, particularly the development of North-South training programs, by providing grants for the trainings of scientist and health worker of endemic countries.
- The promotion of pharmaceutical R&D capacity building in (L)DCs.

5. Fundamental research

The development of a national strategy to support the continuous basic and translational research for neglected diseases.

This may be of particular importance for Switzerland because of the strong involvements of Swiss public research institutions (particularly the Swiss Tropical Institute, as well as the Global Health Institute) in this research and, the option to increase and further develop excellence

within this field. The strategy may contain the development of a special R&D program for neglected diseases within the research and science policy; the development of a national research program under the framework of the Swiss National Science Foundation (SNF); the development of a framework that facilitates the Swiss participation in international programs such as the European and Developing Countries Clinical Trials Partnership (EDCTP); and the consideration of increased support of North-South scientific collaborations related to neglected diseases, for example through the channel of the SNF.

6. Development cooperation

The responsibilities of the Swiss Development Cooperation (SDC) includes the support of the socio-economic development of (L)DCs. Ill health influences the socio-economic development of both the affected individuals and the endemic countries. Thus, public health issues of (L)DCs, and as such neglected diseases, should be developed in the framework of the SDC. The creation of a structure that would be exclusively responsible for (L)DC public health concerns within the Swiss Agency for Development and Cooperation should be considered. Furthermore, the financial resources of the Agency need to be increased in order to contribute to international neglected diseases health programs and initiatives according to their scope and importance (also including in particular the funding of PDPs).

7. Development of a neglected diseases network structure in Switzerland

Switzerland has an excellent medical, biotechnological and pharmaceutical R&D environment. It should develop a strategy to link all actors by creating a network structure of all Swiss-based stakeholders active in the field of neglected diseases to provide them with a platform for interaction, discussion, information and other related activities.

PART ONE

Analysis of the current international neglected diseases R&D environment

A. Introduction

I. Neglected diseases

1. Definition of the term "neglected diseases"

The term "neglected diseases" is used in different ways to describe the issue of lack of attention given by national and international public health agendas and pharmaceutical research and development (R&D) of products for diagnosis, prevention and treatment of certain diseases. The definition in its broadest scope considers as "neglected" all diseases for which there is no commercial market to perform R&D in medical products for prevention and treatment. This may include, for example, rare diseases that affect only a small patient population in high-income countries, but also tropical infectious diseases with high predominance in low- and middle-income countries. In the international debate, the term is used in respect of diseases that disproportionately affect developing countries. Focusing on a classification of diseases with potential importance for least developed and developing countries ((L)DCs), the WHO Commission on Macroeconomics and Health (CMH) Report of 2001[1] created three categories of types of diseases: (1) Type I diseases that are incident in both rich and poor countries, with a large vulnerable population in each, for example non-communicable diseases such as diabetes or cardiovascular diseases, and communicable diseases such as hepatitis B or measles; (2) Type II diseases that are incident in both rich and poor countries, but with a much higher predominance in the poor countries, for example HIV/AIDS, or tuberculosis; (3) Type III diseases as diseases that predominately or exclusively occur in (L)DCs, such as leishmaniasis, onchocerciasis (African river blindness), or African trypanosomiasis (sleeping sickness). Type II diseases are considered as "neglected diseases" in terms of pharmaceutical product development, while Type III diseases are described as the "most neglected diseases". The World

[1] WHO Commission on Macroeconomics and Health, Investing in health for economic development, 2001, pp. 23 ff.

Health Organization (WHO)[2] concentrates on the latter in its Programme "Control of Tropical Neglected Diseases", and defines "neglected diseases" as "diseases affecting almost exclusively poor and powerless people living in rural parts and urban slums of low-income countries". In a non-exhaustive list, the organization includes about 14 tropical infectious diseases, such as Buruli ulcer, Chagas disease, soil-transmitted helminthiasis or leishmaniasis[3].

The poverty of the affected populations and the predominance in (L)DCs are key features of these last mentioned categorizations of diseases, while the lack of pharmaceutical products to prevent or treat these illnesses is implicit.

2. Specification of the neglected diseases in this study

Referring to the categories created by the WHO CMH, which have also been adopted by the WHO Commission of Intellectual Property, Innovation and Public Health (CIPIH) in its report of 2006[4], the underlying study focuses on the "poverty related" Type III diseases as described above with the key features that they predominately affect poor populations in (L)DCs, for which health R&D and interventions are regarded as inadequate.

The Type I and Type II conditions are prevalent in both industrialized and (L)DCs, in the latter case, however, disproportionately in the poor regions. The CIPIH Report suggests an increasing prevalence of non-

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[2] WHO Strategic and Technical Advisory Group on Neglected Tropical Diseases (STAG), Report of the first meeting of the WHO Strategic and Technical Advisory Group on Neglected Tropical Diseases, April 2007, p. 1.

[3] Buruli ulcer, Chagas disease, cholera/epidemic diarrhoeal diseases, dengue/dengue haemorrhagic fever, dracunculiasis (guinea-worm), endemic treponematoses (yaws, pinta, endemic syphilis), human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy, lymphatic filariasis (elephantitis), onchocerciais (river blindness), schistosomiasis, soil-transmitted helminthiasis, and trachoma, *see* WHO Global Plan to Combat Neglected Tropical Diseases, 2008-2015 (WHO/CDS/NTD/2007.3), p. 2.

[4] Report of the Commission on Intellectual Property Right, Innovation and Public Health (CIPIH), Public health, innovation and intellectual property rights, April 2006 [hereinafter CIPIH Report, 2006].

communicable conditions (such as diabetes or cardiovascular diseases) in (L)DCs, causing, in contrast to the high-income countries, a double burden for the poor regions in combination with the high incidence of the communicable diseases[5]. For the Type I and II diseases, the R&D of pharmaceutical products is assured by the therapeutic markets in high-income countries alone, while the potential recovery of R&D costs in the low- and middle- income countries does not have a particular share in the R&D investment decisions. From a public health perspective, basic issues in these fields imply that health interventions developed for high-income markets are often technically not adapted to the conditions in (L)DCs, or not affordable for affected populations. The international debate has focused on the problem of impaired access to health measures to diagnose, prevent or treat that are provided in the high-income countries, however, for several reasons, are not distributed in low- and middle-income regions. This fundamental and urgent problem cannot be overlooked and will require particular attention and solution finding at the international level.

The remit of the underlying study, however, is to cover the range of diseases and conditions that overwhelmingly or exclusively affect (L)DCs and innovation of health technologies that is not stimulated by a market in industrialized countries. Prevalent in specific geographical areas and related to certain environmental conditions, they are not perceived as a direct threat to high-income countries. Their rather low mortality rate, in comparison to other diseases such as HIV/AIDS, reduces their status as primary public health problem at the international level, and they receive less attention and funds, as well as, often, low priority in the agendas of development cooperation agencies[6]. The incidence of the Type III diseases in regions with little or non-existing markets due to the lack of financial power of governments and populations makes them less viable for commercial R&D. This study focuses on the examination of the lack of sufficient incentives for the product development of new diagnosis,

[5] *Ibid.*, p. 3.

[6] WHO, Intensified control of neglected diseases, Report of an International Workshop, Berlin 2003, 10-12 December 2003, Geneva 2004 (WHO/CDS/CPE/CEE/2004.45), p. 6.

prevention and treatment technologies and the potential interventions to address this failure. The neglected diseases covered under this analysis are primarily those 14 identified from the list of the WHO Programme "Control of Tropical Neglected Diseases "(see paragraph I.1.). While HIV/AIDS is often described as a neglected disease, the major financial and infrastructure investments in this therapeutic field appears to make it inappropriate to continue with the designation, even if the challenges faced in this field remain vast. Tuberculosis and malaria also receive increased international attention and allocation of research resources. Although predominately incident in (L)DCs and affecting primarily poor and marginalized patients, these illnesses may nevertheless provide a threat to high-income countries. The closeness to regions with high prevalence in the case of tuberculosis, and the travel market and military in the case of malaria, create some commercial incentives for product development. The market for health technologies to diagnose, prevent and treat these illnesses, however, remains small in high-income countries. Thus, both diseases are also included in the remit of this study, as far as the issues and conclusions drawn in the analysis could equally be considered for Type III diseases and tuberculosis and malaria.

3. Prevalence and global burden of neglected diseases

Neglected diseases result in more than 530.000 deaths annually and the burden of disease in disability adjusted life years as a metric is 56.6 million[7]. They often result in severe and permanent disabilities (for example, impaired childhood growth, mental retardation, blindness, amputation) and deformity and only some of them are life-threatening if left un-

[7] The Disability Adjusted Life Year or DALY is a health gap measure that attempts to combine both the time lived with disability and its long-term impact and the time lost due to premature mortality. One DALY can be thought of as one lost year of 'healthy' life and the burden of disease as a measurement of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability. Definition of the World Health Organization. At http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/index.html, accessed on 16 January 2009. Numbers are taken from Hotez P.J., Molyneux D.H., Kumaresan J., Ehrlich Sachs S., Sachs J.D., Savioli L., Control of neglected tropical diseases, N Engl J Med 357 (10), September 2007, pp. 1019, 1021.

treated, such as visceral leishmaniasis. According to an estimation by WHO, approximately one billion people suffer from one or more neglected diseases. More than 140 countries and territories (most of them in Central and South America, South East Asia and, in particular, sub-Saharan Africa) are afflicted by at least one neglected disease and more than 70 percent of them are low- or lower middle-income countries affected by two or more illnesses. 28 countries suffer under the prevalence of more than six diseases simultaneously, most of them being low-income economies and under humanitarian emergencies[8]. Emerging parasite resistance and HIV-leishmaniasis co-infection aggravates the difficulties.

Poverty and neglected diseases are interrelated. The highest infection rate concentrates on poor and marginalized populations living in impoverished settings in rural remote areas or slums. Determinants of poverty, such as poor housing conditions and sanitation, lack of access to clean water, poor diet and malnutrition, lack of basic health care and others increase the risk factors of disease development and delay or inhibit appropriate diagnosis and treatment. Children, women, ethnic minorities or displaced people as a result of war[9] are the most vulnerable population groups. Stigmatization and discrimination associated with neglected diseases cause social disadvantages and may lead to loss of social and economic support for the affected individual. Neglected diseases, moreover, adversely affect productivity and welfare of patients, their families or whole communities. Affected persons not only suffer from the disease conditions, but also face income losses because of the illness; they have to carry the burden of treatment costs, which again increases impoverishment. In endemic countries (such as the sub-Saharan African coun-

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[8] WHO, Neglected Tropical Diseases – Hidden success, Emerging opportunities, 2006. Available at http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_2006.2_eng.pdf, accessed on 11 November 2008.

[9] For example, the epidemic of visceral leishmaniasis in Sudan, which caused a mortality of up to 36 percent, has been induced by population displacement as a result of war, drought and famine. *See* Seaman J., Mercer A.J., Sondorp E., The epidemic of visceral leishmaniasis in western Upper Nile, southern Sudan: course and impact from 1984 to 1994, International Journal of Epidemiology 1996, Vol. 25, pp. 862-71.

tries) the high prevalence of neglected diseases has multiple effects on productivity, demography and education, leading to severe impediments to long-term socioeconomic development of the burdened country[10].

II. Pharmaceutical innovation and neglected diseases

1. Availability of adequate treatments for neglected diseases

Availability and accessibility of appropriate treatments vary from one neglected disease to another. For some diseases, low-cost and easy-to-use health tools exist and are embedded in national and international control programs. Examples are lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthes, all caused by parasitic worms.

The transmission of lymphatic filariasis[11] can be halted by treating infected persons with donated medicines[12] once a year, for four to six years with a single dose combination of oral drugs[13]. For onchocerciasis[14], a single annual dose treatment exists, also provided as donation by the pharmaceutical manufacturer[15]. Schistosomiasis and soil transmitted helminthiasis affect about 300 million individuals, primarily school-age

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[10] WHO Commission on Macroeconomics and Health, Investing in health for economic development, 2001, pp. 23 ff [hereinafter WHO CMH 2001].

[11]The disease, also known as elephantiasis, is a painful disfiguring disease that causes damages to the lymphatic system, the kidneys, arms, legs and genitals. Transmitted through mosquitoes around 120 million people are affected and about 1.3 billion people in 80 countries are estimated at risk for infection. WHO webpage, Lymphatic filariasis, at http://www.who.int/lymphatic_filariasis/en/, accessed on 1 September 2009.

[12] For example, Albendazole provided by GlaxoSmithKline in unlimited quantities for the Global Programme to Eliminate Lymphatic Filariasis (launched in 2000 with the aim to eliminate the disease by 2020).

[13] Caines K., Global health partnerships and neglected diseases, GHP Study Paper, DFID Health Resource Centre, 2004, p. 12.

[14] The disease is also known as river blindness and causes severe visual impairments, including permanent blindness, skin lesions and a reduction of life expectancy of infected individuals by up to 15 years. *See* WHO Neglected Tropical Diseases, Preventive chemotherapy and transmission control, WHO/CDS/NTD/2006.3a, 2006, p. 3.

[15] Ivermectin, donated by Meck & Co.

children, and may lead later to chronic irreversible disease such as liver fibrosis, cancer of bladder or kidney failure[16]. The infections can be prevented by annual single dose of an existing medicament, and can be treated with the product[17].

Problems remain, in particular, in encouraging continuous R&D of alternative treatments to avoid resistance; in ensuring the sustainable financing for the continuation of the prevention and treatment programs, as well as in exploiting the possibilities offered by existing treatments, due to lack of national priority or adequate distribution systems for the drugs and health personnel to provide them to all affected populations, also in remote rural areas.

Other neglected diseases, such as African trypanosomiasis, Dengue fever, or Chagas disease, however, lack safe, affordable, or modern effective health tools. Patients are often treated with old drugs limited by toxicity and serious side effects or inadequate administration modes that are less suitable for the difficult health infrastructure conditions in (L)DCs. A typical example is the current second stage[18] treatment for African trypanomiasis consisting of two drugs: Melarsoprol (in use since 1949), derived from arsenic, has many severe side effects, including development of encephalopathy (encephalopathic syndrome) which can be fatal; the Eflornithine is less toxic, however only effective against one form of the disease and difficult to apply[19]. For Dengue fever, or the chronic form of Chagas disease, treatment does not exist at all. Moreover, Buruli ulcer is "poorly understood"[20], health technologies for diagnosis, prevention and

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[16] WHO Neglected Tropical Diseases, Preventive chemotherapy and transmission control, WHO/CDS/NTD/2006.3a, 2006, p. 3.

[17] Parziquantel - donation from Merck & Co. to the WHO.

[18] The second stage of African trypanosomiasis is known as the neurological phase. It begins when the parasite that is transmitted through the bite of an infected tsetse fly crosses the blood-brain barrier and invades the central nervous system. WHO African trypanosomiasis fact sheet. Available at http://www.who.int/mediacentre/factsheets/fs259/en/, accessed on 12 November 2008.

[19] Ibid.

[20] Hunt P., Special Rapporteur on the Right to Health, UN Health and Human Rights Working Paper Series No. 4, Neglected diseases, social justice and human rights: Some preliminary observations, Berlin, December 2003.

treatment are lacking and the disease is addressed by surgery, with lengthy and costly hospitalization for extensive forms.

Hence, simple, more effective diagnosis tools and medicines are required, designed for the application in the resource-poor settings.

2. Lack of pharmaceutical innovation for neglected diseases

Global health R&D expenditures for the year 2005 have been estimated at US $ 160.3 billion[21]. This amount represents the global private and public investments in health research. The largest part of the spending on health R&D comes from high-income countries (97 percent) and a small fraction is carried out by low- and middle-income countries (three percent equaling US $ 5.1 billion in 2005)[22]. The main financial resources for health R&D came from the private sector with 51 percent of the global investments (US $ 94 billion). This includes multinational pharmaceutical companies (MNC), biotechnology and medical instrument firms as the principal actors. Most of these companies are situated in high-income countries and operate in these regions[23].

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[21] Global Forum for Health Research (GFHR), Monitoring financial flows for health research 2008, Prioritizing research for health equity, Geneva 2008, p. xiii [hereinafter GFHR 2008]. The investments in the health research sector have steadily increased up from US $ 125.8 billion in 2003, US $ 105.9 billion in 2001 and US $ 84.9 billion in 1998. *See* GFHR 2008, p. 25.

[22] *Ibid*., p. xvi.

Within high income countries, the United States continue to be the largest investor accounting for 50 percent of the investments in 2005, followed by Japan accounting for ten percent of the global sum, the United Kingdom seven percent, Germany six percent, France five percent and Canada three percent, while, amongst others, Switzerland and Italy accounted for two percent each. Investments from low- and middle-income countries come particularly from the so-called innovative developing countries, such as Brazil, China, India, Argentina, and Mexico. *See* GFHR 2008, p. 29.

[23] *Ibid*., pp. 39, 40.

The investments of the firms were carried out in their home countries, in other high-income countries and about two percent in low- and middle-income countries. Companies based in the United States were the biggest investors on global level (49.5 percent), while firms from Japan, Germany, the United Kingdom, France and Switzerland accounted together for 34.0 percent of the total spending.

The public sector is the second largest contributor to the total investment with 41 percent. Funding of governments is allocated to Official Development Assistance (ODA)[24], higher education and direct investments in R&D. Support to research conducted by the private sector is additionally provided in form of tax deductions, credits and other indirect financial contributions to private sector companies, for example the support of graduate and advanced trainings of researchers and for the laboratories used[25].

Eight percent of the total global health R&D investments (about US $ 12.8 billion) in 2005 came from the private not-for-profit sector, a share that has also steadily increased since 1998[26]. Most of this investment was provided by private foundations and universities in high-income countries for R&D conducted in these countries. Ten percent of the contributions went to low- and middle-income countries. The majority of these international investments came from few foundations such as the Wellcome Trust and the Bill and Melinda Gates Foundation (BMGF)[27].

Despite these high and steadily increasing investments by both the private and public sector, the absence of priority setting in health R&D continues to lead to an imbalanced situation in which less than ten percent of the total public and private financial resources are devoted to diseases affecting 90 percent of the world's population, mainly people living in (L)DCs. Most of the health R&D investments of high-income countries are allocated to the development of products, processes and services tai-

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[24] ODA finances are provided to the field of research through various channels, including by funding universities, nongovernmental organizations, foundations, partnerships or public-private partnerships, or at the international level the UN agencies. For an overview, *see* Figure 4.4. Distribution of ODA and channels to research. *Ibid*., p. 90.

[25] *Ibid*., p. 47.

Including the taxpayers' subsidies to private sector into the overall global investments on health R&D would raise the public sector share from 41 percent to 57 percent, while reducing the private sector part from 51 percent to 35 percent. *Ibid.,* pp. 48 and 45.

[26] In 1998, this sector accounted for US $ 5.9 billion, in 2001 for US $ 8.1 billion, and in 2003 US $ 9.0 billion. *See* GFHR 2008, p. 50.

[27] *Ibid*., p. 51.

lored to the domestic health care market[28] while health research for the poor remains insignificant. Concentrating on commercial markets, global health R&D investment priorities have been set according to the burden of diseases in developed regions, leaving out the burden of diseases in (L)DCs[29]. Of 1556 new developed pharmaceutical products from 1975 to 2004, only one percent has been targeted on neglected diseases[30]. Moreover, assessed for their performance against key indicators, such as efficacy, safety, suitability and affordability, these drugs revealed low overall health value to developing country patients because of lack of affordability for the (L)DCs' patients and lack of suitability of the products for the (L)DCs' environment[31].

The first study on global public and private investment into R&D for new products for neglected diseases published in 2009 found that just over US $ 2.5 billion was spent on these conditions in 2007[32]. The funding came mainly from the public sector (69.4 percent), with the US Government through the National Institutions of Health (NIH) investing just more than 70 percent of the total public spending; the philanthropic funders (21.0 percent), particularly the BMGF and the Wellcome Trust; and

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[28] *Ibid*., p. 27; GFHR, the 10/90 report on health research 2001-2002, Geneva 2002, pp. 89 ff.

[29] Lichtenberg F. R., Pharmaceutical innovation and the burden of disease in developing and developed countries, April 2005, p.16.

[30] Chirac P., Torreele E., Global framework on essential health R&D, The Lancet, May 2006 Vol. 367, p. 1560.

The number of ten new developed drugs for neglected diseases excludes malaria (if added 18 drugs) and tuberculosis (if added 21 drugs). These figures present an update from an analysis done for the period from 1975-1999. The study provided the same result: Only one percent of the new chemical entities marked were for tropical neglected diseases. *See* Trouiller P., Olliaro P., Torreele E., Orbrinski J., Laing R., Ford N., Drug development for neglected diseases: a deficient market and a public-health policy failure, The Lancet, Vol. 359, June 2002, p. 2189.

[31] Moran M., Guzman J., Ropars A., Evans A., Neglected diseases – Doctors can make a difference, British Medical Association, March 2007, p. 9.

[32] Moran M., Guzman J., Ropars A.-L., McDonald A., Sturm T., Jameson N., Wu L., Ryan S., Omune B., Neglected diseases research and development – How much are we really spending?, The George Institute for International Health, February 2009, p. 5 [hereinafter Moran et al., 2009].

the pharmaceutical industry (collectively with 9.1 percent)[33]. The study reveals a high concentration of spending on mainly three diseases, namely HIV/AIDS, malaria, and tuberculosis, with 80 percent of the total amount. All other diseases or diseases groups received by far less attention, with less than 5 percent of the spending contributed to each. For the three kinetoplastid diseases, including sleeping sickness, Chagas and leishmaniasis, funding was 4.9 percent or US $ 125.1 million[34]. For helminth infections (for example, onchocerciasis, lymphatic filariasis, schistosomiasis) two percent (or US $ 51.6 million) of the total funding was used, predominantly allocated by the public sector[35]. Dengue fever received about 3.2 (US $ 82.0 million) percent of the spending, from which just over 40 percent of the amount came from private companies and the US Department of Defense, showing some interest in a commercial Dengue fever market and the protection of military personnel working in endemic areas[36]. Buruli ulcer, trachoma and leprosy received less than US $ 10 million or 0.4 percent of the global investment each[37].

The high concentration of research on HIV/AIDS, tuberculosis and malaria may be influenced particularly by aspects such as the burden of disease, the presence of civil society groups or product development partnerships with active advocacy and fundraising activities; or the presence of policy frameworks and funding mechanisms that prioritize specific diseases. Funding patterns of pharmaceutical companies, as presented in the study, suggest that firms principally respond to commercial signals, but also to public policy strategies and the existence of develop-

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[33] The contributions of the pharmaceutical companies include industry's own investments without the funding provided by product development partnerships or others to industry programs. The majority of the private sector spending went to the three diseases HIV/AIDS, malaria and Tuberculosis, and some spending also on more commercial neglected diseases, such as Dengue fever. *See* Moran et al., 2009, p. 38.

[34] *Ibid*., p. 20. The biggest share of funds for kinetoplastid diseases went to drug development (about 50 percent) and basic research (33.1 percent). Funding was mainly provided by philanthropic foundations and public sector.

[35] *Ibid*., p.24.

[36] *Ibid*., p. 23.

[37] *Ibid*., p. 5.

ment partners or PDPs to collaborate with[38]. The strong focus on the three diseases and the related activities of various actors involved in health R&D, while indispensable and meritorious, nevertheless shows that all other diseases predominately or exclusively affecting (L)DCs still lack the attention of the global research community and still lack funding that is required to discover, develop and register new health products. Moreover, the displayed high predominance of few funding organizations demonstrates the vital role that these groups play in defining the global disease focus and funding patterns for neglected diseases R&D[39]. The reliance on a small number of contributors may additionally endanger sustainability of funding of the neglected diseases R&D when economic uncertainty may influence the interests and investment capacities of the few funding organizations[40]. A broadening of funding efforts to include all possible actors who are able to contribute and to provide adequate funding to all diseases according to the need could provide a significant impact on the health situation in (L)DCs and the affected patients[41].

Finding ways to prioritize R&D in a way that (also) takes into account the underserved health needs of poor populations remains a primary challenge.

3. Pharmaceutical innovation

a) The drug innovation process in industrialized countries

Innovation in the pharmaceutical field is a complicated process of translating basic scientific findings of disciplines such as molecular biology, medicinal chemistry and genomics into therapeutic and diagnostic

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[38] *Ibid*., p. 48.

[39] *Ibid*., p. 48. The NIH as main public funding source predominately provides direct grants to researcher or developers rather than through funding of PDPs. Also, the BMGF as the principal philanthropic funders predominately allocates funding to applied research rather than basic science.

[40] *Ibid*., p. 48.

[41] *Ibid*., p. 49.

products for protection and treatment of multiple diseases. It involves various institutions and organizations at different stages, including the academic environment, government, private pharmaceutical companies (small, medium-sized, large), biotechnology firms, non-profit foundations, diseases control agencies, contract research organizations, and others.

Basic research, often referred to as upstream research, generates the fundamental knowledge to enable transitional research and development of products. It is largely performed by academia and non-profit public research institutes, and funded by governments. This basic research sometimes produces leads that the pharmaceutical industry can use to promote the discovery of new therapeutic compounds. Product development or downstream research is traditionally initiated by private companies. Recent scientific, economic and legal development, however, has influenced the interface of upstream and downstream research and has created greater interaction between different participants in the innovation cycle. Substantial advances in molecular biology, pathophysiology, or the sequencing of genetic material have contributed to the rise of the biotechnology industry. As producers of fundamental knowledge in gene-based techniques, biotechnology and other small companies have become important strategic partner of the pharmaceutical industry. Moreover, changes in laws have allowed universities and public research institutions to extend patenting and licensing policies on publicly funded research and to use intellectual property assets as source of revenue and to promote commercial application[42].

The process of product development (from discovery to market approval) can be divided into discovery, pre-clinical trials, human clinical development (clinical Phases I-III), registration, and post-marketing studies (often referred to as Phase IV trials)[43].

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[42] CIPIH Report, 2006, pp. 38, 39.

[43] Figure adapted from Nwaka S., Ridley R. G., "Virtual drug discovery and development for neglected diseases through public-private partnerships", Nature Review Drug Discovery, 2003: 2, pp. 923-924; and Berndt E.R., Gottschalk A.H.B., Strobeck M.W., Opportunities for improving the drug development process: Results from a survey of industry and the FDA,

The first stage consists of research into the mechanisms and pathogenisis of the particular disease to receive a basic molecular understanding of the illness and identify possible targets as basis for the development of therapeutic substances. The pre-clinical process involves lead compound identification after high-through-put screening of thousands of chemicals or proteins against the specific biological target and lead optimization for pharmaceutical properties. Analysis in animal models is carried out for safety, efficacy and toxicity. Human testing in clinical Phases I-III begins after a successful clinical trial application to the regulatory authority. In Phase I, the drug is tested in a small group of healthy volunteers with the main goal of establishing the safety of the drug in humans. During Phase II, the candidate drug is given to a larger group of volunteers (several hundreds) with the targeted condition in order to evaluate efficacy, safety and tolerability and to determine the optimal dosage range. Phase III involves large groups of people (hundreds or thousands, depending on the therapeutic field and targeted condition). The candidate drug is tested against standard treatment or a placebo, and safety, efficacy and dosages are established. In most cases several Phase III trials are carried out. They take about four years on average and represent the most costly period of drug development. The data and documents produced during the clinical trials are reviewed by the regulatory agency after an application for marketing authorization of the new drug.

Post-marketing studies, or Phase IV trials, are conducted after market approval in order to investigate the long term effects of a drug in a heterogeneous population and to determine further risks, benefits and optimal use of the drug. Depending on the therapeutic condition, the average length of Phase IV studies can be three or four years, for some chronic diseases much longer[44].

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presented at the National Bureau of Economic Research Workshop on Innovation Policy and the Economy, April 2005, p. 9.

[44] *Ibid*.

b) Total time in and costs of pharmaceutical R&D in industrialized countries

Drug development has been described as a time-consuming, expensive and risky process[45]. Moreover, studies show that development times and costs have increased over decades[46]. The total time in drug development is estimated at 10 to 12 years on average. The costs of R&D of a new pharmaceutical product reflect the complex technical process of product development and the costs related to the regulatory approval. An often cited study estimates the total out-of-pocket costs of pre-clinical and clinical development at US $ 403 million per approved new drug[47]. The calculation includes costs of R&D efforts that are unsuccessful because of lack of safety and significant efficacy; poor economic prospects are also included into the calculation. About 70 percent of NCEs survive clinical Phase I and enter Phase II, and approximately 30 percent continue to Phase III. Of the candidate compounds having completed the Phase III, only approximately 20 percent get approval of the regulatory authority[48]. Opportunity cost of capital[49], however, account for almost half of the total estimated R&D costs of US $ 802 million for pharmaceutical product

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[45] Kaitin K.I., Director Tufts Center for the Study of Drug Development, News and Events, May 13, 2003, on http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29; accessed on 3 September 2009.

[46] DiMasi J. A., Hansen R.W., Grabowski H.G., The price of innovation: New estimates of drug development costs, Journal of Health Economics, 22 (2), 2003, p. 165 [hereinafter DiMasi et al., 2003]; Gilbert J., Henske P., Singh A., Rebuilding big pharma's business model, In Vivo, the Business & Medicine Report, Windhover Information, 21 (10), November 2003, pp. 2, 3.

[47] DiMasi et al., 2003, p. 166.

[47] A subsequent study estimates the actual costs for discovering, developing and launching a new drug at nearly US $ 1.7 billion, a 55 percent raise on the average level between 1995 and 2000. Main factor for the increase, as cited in the study, is the decline in R&D productivity, with one in 13 candidate compounds put into preclinical trials now reaching the market. *See* Bain drug economics model, 2003, data from Gilbert J., Henske P., Singh A., Rebuilding big pharma's business model, In Vivo, the Business & Medicine Report, Windhover Information, 21 (10), November 2003, pp. 2, 3.

[48] DiMasi et al., 2003, p. 162.

[49] Opportunity cost of capital embodies the return that shareholders would have received had they invested in activities that generate immediate returns rather than in long-term drug discovery process. Including these costs is standard practice in economic analysis.

development (opportunity cost at US $ 399 million) according to the study. Commercial pharmaceutical companies finance product R&D by private equity capital. This requires the firms to generate a return on the investment to compensate the shareholders.

c) Patents as main incentive model for pharmaceutical innovation

In industrialized countries, drivers for pharmaceutical R&D investments are given by interconnected factors such as a R&D promoting environment, including features such as a strong scientific community, and the existence of public R&D facilities; governmental financial and fiscal policies committed to innovation; an efficient investment environment based on sustainable financing mechanisms, e.g. by venture capital; comprehensive third party payment; and appropriate patent protection for pharmaceutical innovation. As all private sector industries, pharmaceutical R&D investment is market and profit oriented. The pharmaceutical industry business model is characterized by strong reliance on intellectual property protection, particularly through patents. In this highly competitive sector where development programs last for 12-13 years and require significant investments, the industry feels that only the securing of a monopoly can justify the investment of time and funding into the R&D of new drugs. Patents grant exclusive rights on a specific compound for a limited time. The economic rationale, besides creating barriers to market entry for imitating products, is to enable innovative pharmaceutical companies to charge prices above marginal costs and to recover development expenditures from the profits, thus preserving incentives for future R&D. In industrialized countries, these higher expenses are generally covered by third party payments of health insurances. Intellectual property protection, particularly through patents on an invented drug is seen as critical in the pharmaceutical sector because of the low costs of imitation once a product has been developed. The lack of a legal framework for patent protection of products and processes is considered as uneconomical, since adequate protection of the innovation is not guaranteed. The private sector, stimulated by the patent system and market forces, mobilizes considerable resources to develop treatments

where significant markets exist. Where it is not possible to exclude competitors from access to findings, private firms tend to under-invest in R&D. The argument is that no market mechanism can ensure that some of the benefits of the innovation will not be captured by other firms.

From the economical standpoint, granting more valuable patents increases the incentives for R&D, which in the long run results in a higher rate of technical progress. Length and strength of patent protection play an important role, along which patents can be made weaker or stronger. A longer and stronger patent implies a longer lasting exclusivity for a firm; it is more valuable and thus provides a greater incentive for innovation; however, this means, in return, less competition in the post innovation. Furthermore, although pharmaceutical products receive a 20-year period of patent protection like any other innovation in other industries, this duration of protection will be reduced during the process of obtaining the market approval. To protect the investments at an early stage of R&D pharmaceutical inventors in general apply for a patent before starting the clinical trials procedure. As a consequence, the average period of effective patent life (patent life left once the new drug reaches market) had been diminished so much that it threatened the viability of innovative R&D. By the time a product reaches commercialization there may be eight years remaining to recoup the investment and to realize profits. The legislators recognized the need of protection for the high investments into the development of new drugs by pharmaceutical companies to be extended and introduced the supplementary protection certificates, which can take effect for a maximum of five years after expiry of the original patent term and are capable of extending the exclusivity for a particular medicinal product to a maximum of 15 years. Nevertheless, it is still typical for a pharmaceutical product to reach the market with only 10-12 years of patent protection remaining.

4. Challenges in the neglected diseases pharmaceutical R&D

a) Lack of pharmaceutical markets in (L)DCs

The interaction between public and private competences, interests and investments in the pharmaceutical innovation sector has created a reasonable supply of medicinal products and tools of societal needs in industrialized countries, providing a substantial public health benefit for a variety of therapeutic categories. Market-based incentives such as patent protection have been completed by additional push and pull measures to support the development of health technologies, in areas with low profitability expectations such as orphan diseases. Much of the pharmaceutical innovations generated in response to expectations of sales and cost recovery has also contributed to improved health in (L)DCs[50]. However, these benefits arising from products developed for industrialized countries represent spill-overs of focused R&D for economically viable markets. Under the current innovation system for pharmaceutical R&D, decisions and strategies are based on market conditions that fail to generate incentives for the R&D of products, where viable economic markets do not exist, as assumed for example in (L)DCs (see also chapter II.2).

Pharmaceutical markets require physical infrastructure in form of warehouse facilities to store inventory; roads for efficient transportation; an efficient distribution system; social and institutional infrastructure such as hospitals and trained personnel for drug distribution; and, above all, an effective consumer demand manifested in the willingness to pay and ability to pay[51]. The majority of countries with high neglected diseases epidemics lack most or all of these factors, while the lack of purchasing power of and for patients appears to be the main disincentive. The size of

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[50] For example, the WHO Expanded Programme of Immunization (EPI) provides three-quarter of the world's children with standard treatment of cheap, safe, effective, off-patent vaccines against several diseases such as measles or maternal or neonatal tetanus.

Information taken from UNICEF- Expanding immunization coverage: http://www.unicef.org/immunization/index_coverage.html; and the WHO Expanded Immunization Programme: http://www.wpro.who.int/sites/epi/overview.htm, accessed on 2 September 2009.

[51] Hammer P.J., Differential pricing of essential AIDS drugs: Markets, politics and public health, Journal of International Economic Law (2002), p. 888 [hereinafter Hammer, 2002].

the developing country market is large, accounting for 78 percent of world population and 85 percent of world DALYs[52]. Nevertheless, the fact that only very few drugs were approved for tropical diseases provides evidence that few viable economic markets exist in (L)DCs. Objective needs of millions of patients do not automatically convert into effective market demand[53]. Most (L)DCs have limited health insurance coverage and purchases of pharmaceuticals are out-of-pocket expenditures for patients. Expectation of low prices because of low per capita income and weak reimbursement policies distort effective demand and profitability expectations of the private pharmaceutical sector. For drugs found in (L)DCs only, the prices affordable by the patients in those countries are not sufficient to bear R&D costs, thus to spur pharmaceutical innovation for the poor[54].

b) Challenges in the pharmaceutical R&D process for neglected diseases

Despite small markets and limitations of the pharmaceutical industry business model for product development for neglected diseases, the research for these conditions also faces challenges beyond the generic complexity in producing new remedies for illnesses. Gaps occur throughout the product development line. First, existing fundamental research on the diseases and the various parasites causing them has often not been turned into knowledge for further development into a product for testing and clinical experiments. Generally, basic research is generated by publicly funded research institutions. Pharmaceutical companies obtain this knowledge from those organizations if it correlates with the firms' focus on specific pharmaceutical areas. Science that is of little interest for the focused and targeted product development remains at the

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[52] Lichtenberg F. R., Pharmaceutical innovation and the burden of disease in developing and developed countries, April 2005, p. 16.

[53] Hammer, 2002, p. 888.

[54] Danzon P. M., Towse A., Differential pricing for pharmaceuticals: Reconciling Access, R&D and patents, International Journal of Health Care and Economics, 3 (3), 2003, p. 184 [hereinafter Danzon P.M., Towse A., 2003].

observation stage without translating into applicable technology. Moreover, due to lack of interest of the research community, latest advances in science and technologies in drug discovery, such as pharmacogenomics or high throughput screening, have not been exploited for the neglected diseases, resulting in a gap in the identification of new biological targets to generate new compounds that could be further developed into health products[55].

Second, even if a compound for a neglected disease has been identified by screening, molecular modification, rational design or serendipity and analysis in animal models for safety, efficacy and toxicity proves successful, the validated targets are often not carried into the clinical development because of profitability evaluations of the diseases in relation to the high costs of the clinical trial phases.

Third, conducting the clinical experiments, which involve the testing of the substances on humans in (L)DCs, frequently represents particular challenges for product developers. Resource constraints exist in all areas in most (L)DCs, including the lack of clinical trial infrastructures in terms of health facilities, clinicians, technicians and the management of clinical data; the lack of regulatory capacities to provide approval for clinical trials and for the successfully developed health technology; and the lack of ethical review capacities, including skilled and quality ethical review committees[56]. Practical and ethical regulatory problems can also arise from the poor literacy of affected patients and the different cultural environments. These factors may complicate, for example, the ability to gain informed consent, or carry the risk of being insensitive to local cultural

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[55] Nwaka S., Ridley R. G., Virtual drug discovery and development for neglected diseases through public-private partnerships, Nature Review Drug Discovery, 2003: 2, pp. 923-924.

[56] TRREE for Africa (Training and Resources in Research Ethics Evaluation for Africa) is one program example established to increase knowledge and practical skills of those involved in the management and conduct of ethics evaluation and partnerships in Africa. It is a web-based training and capacity building initiative on ethics of research involving humans conducted in African countries. Besides the strengthening of research ethics evaluation capacities in Africa, it further aims to foster lasting partnerships amongst and with African partners, as well as to create of a platform to facilitate dissemination of knowledge in Europe and Africa. *See* TRREE for Africa webpage at http://elearning.trree.org/, accessed on 16 September 2009.

traditions, and socio-economic aspects[57]. To address this gap in clinical trial capacities in (L)DCs, a new initiative was established in 2001, the European and Developing Countries Clinical Trial Partnership (EDCTP) that aims to accelerate the development of new or improved drugs, vaccines and microbicides against HIV/AIDS, malaria and tuberculosis, with a focus on phase II and III clinical trials in sub-Saharan Africa[58]. Amongst others, the program activities also include the development and strengthening of capacities in (L)DCs, the promotion of technology transfer, the encouragement of the participation of the private sector, and the mobilization of additional funds to fight the specified diseases. Further conditions disproportionately affecting (L)DCs, other than the three identified diseases, are, however, not included into the initiative.

The lack of delivery structures in (L)DCs for the developed health products is a last challenge in the field of neglected diseases. To be effective, innovation of needed health technologies also requires physical access to the products for the affected patients. Most affected people live in remote rural areas under difficult life conditions with lack of or inadequate health facilities. Health systems in the endemic countries are often resource-constrained and lack basic infrastructure, skilled personnel in adequate number, and functioning healthcare delivery systems which are essential to making existing health products available[59].

B. Relevant international legal frameworks

The state of health has fundamental effects on the social and economic development of both the individual and the society. During the last two decades, health emerged as an important topic at the international level, and the international community increasingly has recognized the impact of health on development. Particularly the public health issues of resource-poor countries and impoverished populations attracted the global

[57] CIPIH Report, 2006, pp. 96, 97.

[58] EDCTP webpage. At http://www.edctp.org/, accessed on 3 September 2009.

[59] CIPIH Report, 2006, pp. 115, 119.

attention and awareness and led to the generation of major global health initiatives such as the Joint United Nations Programme on HIV/AIDS (UNAIDS)[60], the Global Fund to Fight AIDS, Tuberculosis and Malaria[61], or the Roll Back Malaria Partnership[62]. The begin of the 21st century also saw the launch of not-for-profit organizations, set up to accelerate the development of health technologies for diseases predominately affecting (L)DCs, including the Medicines for Malaria Venture[63], or the Drugs for Neglected Diseases initiative[64]. Increasingly, global health is recognized as an essential element of foreign policy[65].

Public health concerns of (L)DCs, and as such neglected diseases, have also been on the agendas of various international forums.

I. International human rights law

Embodying neglected diseases in the context of international human rights law, the core provisions connected to the issue of R&D for neglected diseases are the fundamental human right to the highest attainable standard of health as expressed in the article 25 of the Universal Declaration of Human Rights (UDHR) and article 12 of the International Covenant on Economic, Social and Cultural Rights (ICESCR), as well as the right to enjoy the benefits of scientific progress and its application (article 15 ICESCR).

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[60] http://www.unaids.org/en/default.asp

[61] http://www.theglobalfund.org/en/

[62] http://www.rollbackmalaria.org/

[63] http://www.mmv.org/rubrique.php3?id_rubrique=15

[64] http://www.dndi.org/

[65] Chan M., Støre J.G., Kouchner B., Foreign policy and global public health: working together towards common goals, Bulletin of the World Health Organization, July 2008, 86 (7), p. 498; Kickbusch I., Erk C., Global health diplomacy: The new recognition of health in Foreign policy, in Clapham A., Robinson M., Mahon C., and Jerbi S., Realizing the right to health, Swiss Human Rights Book Vol. 3, 2009, p. 517; Donaldson L., Banatvala N., Health is global: proposals for a UK Government-wide strategy, The Lancet 2007 (369), pp. 857-861. Ministers of Foreign Affairs of Brazil, France, Indonesia, Norway, Senegal, South Africa, and Thailand, Oslo Ministerial Declaration – Global Health: A pressing foreign policy issue of our time, The Lancet, 2007, pp. 1373-1378.

1. The right to the highest attainable standard of health

The right to the highest attainable standard of health is a fundamental human right. It is enshrined in a number of international human rights instruments. As first international body, the WHO proclaimed in the Preamble of its Constitution in 1946 that "*the enjoyment of the highest attainable standard of health*" as "*one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition*". Article 25 para. 1 UDHR asserted the protection of health as basic human right[66] and laid the foundation for its legal framework. In the aftermath, the international community set out the concept, among others in a number international standards developed for specific population groups, such as for the protection of persons with mental illnesses or the protection of health in various situations, environments and processes, such as armed conflict, or the workplace. The right to the highest attainable standard of health has been further elaborated by the United Nations Human Rights Council and within human rights special procedures, including the appointment of an independent expert as United Nations (UN) Special Rapporteur in 2002 to investigate, amongst others, specific health and human rights relevant themes and to report on the related human rights interferences[67]. The resolutions of the UN Commission on Human Rights on access to medication, and the guiding litera-

[66] Article 25.1 states that "Everyone has the right to a standard of living adequate for the health of himself and of his family, including food, clothing, housing and medical care and necessary social services…".

The freedoms and entitlements enshrined in the declaration are not subject to ratification by States and do not have legal standing. The effect of the UDHR in its more than 60 years of existence, however, has exceeded its initial conception as an articulation of shared values of all peoples and all nations. In contemporary international human rights law the UDHR carries the status and authority of international customary law and its basic principles are reflected in countless international legal instruments as well as in regional and national legal frameworks.

[67] UN Commission on Human Rights, The right of everyone to the enjoyment of the highest attainable standard of physical and mental health, Resolution 2002/31, 22 April 2002 (EC/2002/23 – E/CN.4/2002/200).

ture developed for health issues such as HIV/AIDS are also of global relevance to influence international and national policy[68].

Additionally, the right to the highest attainable standard of health was adopted in regional human rights treaties[69] and has been part of regional human rights mechanisms adjudicate cases[70]. The foundational international and regional instruments have also influenced health-related provisions in many national constitutions[71] that, in turn, generated important jurisprudence on the subject matter[72].

As a legally binding international instrument, the ICESCR enshrines the "right of everyone to the enjoyment of the highest attainable standard of physical and mental health" in its article 12 para. 1, while article 12 para. 2 illustrates a number of steps to be taken by Parties to achieve the

[68]Commission on Human Rights resolution on the highest attainable standard of health 2002/31 of 22 April 2002; Commission on Human Rights resolution on access to medication 2002/31 and 2002/32 of 22 April 2002; Commission on Human Rights, International Guidelines on HIV/AIDS and Human Rights of January 1997 (UN Doc. E/CN.4/1997/37), in a consolidated version of 2006 at http://www2.ohchr.org/english/issues/hiv/guidelines.htm, accessed on 7 September 2009.

[69] For example: the European Social Charter (of 1961 as revised in 1996); the African Charter on Human and Peoples' Rights (1981); the Additional Protocol to the American Convention on Human Rights in the Area of Economic, Social and Cultural Rights (1988).

[70] *Lopez Ostra v. Spain*, European Court of Human Rights 1994 (Application no. 16798/90); Jorge *Odir Miranda Cortez et al. V. El Salvador*, Interamerican Commission on Human Rights, Case 12.249, Report No. 29/01, OEA/Ser.L/V/II 111 Doc. 20 rev. at 284 (2000).

[71] More than 115 countries have introduced the right to the highest attainable standard of health or health care into their domestic constitutional law either as statement of aspiration, of entitlement, of duty to provide health care, or as programmatic, or referential statement to any international or regional human rights treaty recognizing a right to health or health care. *See* WHO and Office of UN High Commissioner on Human Rights, The Right to Health, Fact Sheet No. 31, June 2008, p. 10; and Kinney E.D., Clark B. A., Provisions for health and health care in the Constitutions of the world, Cornell International Law Journal, 2004, pp. 3, 4.

[72] For example, *Minister for Health v. Treatment Action Campaign,* Constitutional Court of South Africa, July 2002, Case CCT 8/02, para. 135 (2) (a) on the restrictions of the provision of anti-retroviral drugs to HIV positive pregnant women, resulting in tens of thousands of unnecessary infections and deaths, alleging the violation of the right to health care services in s. 27(1) and s. 28(1)(c) of the South African Constitution, and whether there is an unrestricted right to minimum core medical services;

full realization of this right, such as ensuring prevention, treatment and control of diseases (article 12 para. 2. (c) ICESCR)[73].

The scope and dimensions of this broad concept were outlined in greater details by the Treaty monitoring body, the Committee on Economic, Social and Cultural Rights (CESCR) in its General Comment No. 14 on Article 12. The right to the highest attainable standard of health is not to be understood as right to be healthy, but rather as the right to the enjoyment of a variety of facilities, goods, services and conditions necessary for the achievement of the highest attainable standard of health[74]. It is further an inclusive right extending not only to timely and appropriate health care, including access to essential medicines as defined under the WHO Action Programme on Essential Drugs[75], but also to the underlying determinants of health, such as access to safe and potable water and adequate sanitation[76]. The right to the highest attainable standard of health provides freedoms (right to be free from discrimination and non-consensual medical treatment) and entitlements (right to a system of health care and protection). Key elements applicable to the right in all its forms and at all levels are the availability, accessibility, and acceptability of good quality health services, goods, and facilities[77]. Non-

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[73] Article 12 ICESCR: "(1) The State Parties to the present Covenant recognize the right of everybody to the enjoyment of the highest attainable standard of physical and mental health. (2) The steps to be taken by the States Parties to the present Covenant to achieve the full realization of this right shall include those necessary for: (a) The provision for the reduction of the stillbirth-rate and of infant mortality and for the healthy development of the child; (b) The improvement of all aspects of environmental and industrial hygiene; (c) The prevention, treatment and control of epidemic, endemic occupational and other diseases; (d) the creation of conditions which would assure to all medical services and medical attention in the event of sickness. "

[74] Committee on Economic, Social and Cultural Rights (CESCR), General Comment No. 14 on Article 12 of the International Covenant on Economics, Social and Cultural Rights of 16 December 1966. "The right to the highest attainable standard of health", 2000 (UN Doc. E/C.12/2000/4), para. 8, 9 [hereinafter CESCR, General Comment No. 14].

[75] WHO Essential Medicines and Pharmaceutical Policies, at http://www.who.int/medicines/en/, accessed on 19 September 2009.

[76] CESCR, General Comment No. 14 para. 11.

[77] *Ibid*., para. 12.

Availability means that functioning public health and health care facilities, goods and services, as well as programs have to be available in sufficient quantity within the State party.

discrimination and equal treatment are among the most critical components of the right to the highest attainable standard of health. Human rights law proscribes any discrimination in access the health care and the underlying determinants of health on the internationally prohibited grounds, such as race, social origin, and sex that has the intention or effect of impairing the equal enjoyment of the right to the highest attainable standard of health[78]. Special attention needs to be given to the vulnerability of certain groups such as women, children and older persons, or persons with disabilities and others[79]. Based on the limited availability of resources in the individual member countries, the right to the highest attainable standard of health is subject to progressive realization. This means that States have a specific and continuing obligation to move as expeditiously and effectively as possible towards the full realization of the right.[80] Further, States have the legal obligations to respect, protect and fulfill the right to the highest standard of health[81].

The primary duty bearers for implementing this right are the national authorities in the country in question. The State Parties are required to progressively realize the right to the highest attainable standard of health individually, and through international assistance and cooperation according to article 2(1) ICESCR. International assistance does not

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The precise nature of the facilities, goods and services will vary depending, amongst others, also on the development level of the country. Accessibility to health facilities, goods and services includes non-discriminating and physical access, as well as affordability (economic accessibility), and the right to seek, receive and impart information and ideas concerning health issues. Acceptability requires that health facilities, goods and services must be respectful of medical ethics and culturally appropriate, and moreover, scientifically and medically appropriate and of good quality.

[78] *Ibid*., para. 18, 19.

[79] *Ibid*., para. 20-27.

[80] *Ibid*., para. 31.

Some obligations, however, have immediate effect, notwithstanding resources constraints and progressive realizations. This includes the guarantees of non-discrimination and equal treatment, as well as the obligation to take deliberate, concrete and targeted steps towards the full realization of the right to health, such as the preparation of a national public health strategy and plan of action. *Ibid.,* para. 30, 43.

[81] *Ibid*., para. 35-37.

encompass only financial and technical assistance provided by States in the position to assist, but also to respect the enjoyment of the right to the highest attainable standard of health in other jurisdictions, and to make sure that the right is given due attention in international agreements[82].

2. Neglected diseases in the context of the right to the highest attainable standard of health

a) Human rights relevance of neglected diseases

The framework of the right to the highest attainable standard of health developed by the CESCR has been further elaborated by the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health with respect to the issue of neglected diseases[83] and essential medicines[84].

The lack of access to existing health products for poor populations in (L)DCs in terms of physical availability and affordability, and the lack of R&D related to diseases predominately or exclusively affecting the resource-limited regions have human rights relevance[85]. Despite increasing levels of global investments in pharmaceutical R&D, the outcome of new compounds marketed for (L)DCs diseases remains marginal. From the total expenditures in health research by the public and private sectors, only a few percents are directed at the health problems of (L)DCs (see chapter A. II. 2.), displaying a striking disparity between health needs

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[82] *Ibid*., para. 39-40.

[83] Hunt P., UN Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, Neglected diseases: A human right analysis, TDR, Special topics in social, economic and behavioral research report series No. 6, WHO 2007 (TDR/SDR/SEB/ST/07.2), [hereinafter Hunt, 2007]; furthermore, Hunt P., Neglected diseases, social justice and human rights: Some preliminary observations, Health and human rights working paper series No. 4, December 2003 [hereinafter Hunt, 2003].

[84] Hunt P., Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, September 2006 (UN Doc. A/61/338) [hereinafter Hunt, 2006].

[85] Hunt P., The right of everyone to the enjoyment of the highest attainable standard of physical and mental health, Report of the Special Rapporteur, February 2003 (UN Doc. E/CN.4/2003/58), p. 19.

and research investments between countries. Initiatives have been established to address this imbalance in R&D for diseases affecting (L)DCs. However, they remain strongly underfunded.

Involved human rights dimensions include non-discrimination, the availability and accessibility of (essential) medicines, the right to enjoy the benefits of scientific progress (article 15 ICESCR), and international assistance and cooperation (article 2 para.1 ICESCR)[86].

Non-discrimination and equal treatment are fundamental principles of international human rights law. Nobody should be discriminated on the basis of the various status aspects such as race, color, sex, social origin[87], age, and health status[88]. Nations are expected to ensure human rights protection equally for all, and to provide equal opportunities for all, regardless the differences. This includes placing a particular emphasis on vulnerable persons and groups in society, such as women, children, racial and ethnic minorities, who are often socially and economically disadvantaged and marginalized[89].

Discrimination and social stigmatization are in many cases both causes and consequences of neglected diseases[90]. The populations most affected by the infectious conditions are, in general, the vulnerable, poor and marginalized groups living in resource-constrained countries or areas. Based on their ill health status people are often exposed to social inequities, as well as discrimination by public authorities and private actors. Physically disabling and disfiguring conditions produced by diseases

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[86] Hunt P., Report of the Special Rapporteur, Mission to the World Trade Organization, March 2004 (UN Doc. E/CN.4/49/Add.1), p. 13 [hereinafter Hunt, 2004].

[87] Article 2 UDHR.

[88] CESCR General Comment No. 6 on the economic, social and cultural rights of older people, 1995 (UN Doc. E/1996/22), para.11-12; General Comment No. 3 on the nature of States parties' obligations, Article 2 para. 1 ICESCR, 1990 (UN Doc. E/1991/23), para. 9.

[89] Human Rights Committee, General Comment No. 18: Non-discrimination, 1989 (UN Doc. 10/11/89), para. 7 and 13; International Federation of Red Cross and red Crescent Societies and François-Xavier Bagnoud Center for Health and Human Rights, Human rights: An introduction, in Mann J.M., Gruskin S., Grodin M.A., and Annas G. J. (eds.), Health and human rights, 1999, p. 22.

[90] Hunt, 2007, p. 23.

such as leishmaniasis or lymphatic filariasis may be reason for discrimination in the workplace, education and access to health care. This includes particularly women, due to their status in many countries and their lacking ownership of resources that create obstacles to access to prevention and treatment[91]. Moreover, social stigma is often associated with neglected diseases in many societies based on fears, stereotypes and prejudices stemming from cultural and traditional beliefs or misconceptions about origins, transmission and effects of these diseases. Infected people may hide the disease and delay or reject treatment[92].

b) Responsibilities of States

Medical care, prevention, treatment and control of diseases, are core elements of the right to the highest attainable standard of health. These components highly depend upon the availability and accessibility of health technologies. According to the analytical framework provided by the CESCR, the responsibilities of States include ensuring that health products (for neglected diseases) are available, accessible, culturally acceptable and of good quality.

Where safe and quality medicines exists, as suggested, for example, for neglected diseases such as lymphatic filariasis, or Onchocerciasis, all efforts must be made to ensure that the health products are available in sufficient quantities, in all parts of the country, including remote rural areas or urban centers, without discrimination on any of the prohibited grounds, and affordable, including for the poor populations. States, as the principal duty bearer, may be required to design outreach programs to supply all patients with the necessary medicines or to find funding and pricing arrangements to support the affordability for poor affected persons. Medicines must also be of good quality. To ensure this, the es-

[91] *Ibid*.

[92] *Ibid*., p. 24.

tablishment of a regulatory system might be important, for example, to detect counterfeit or tampered medicine[93].

Some neglected diseases such as Chagas diseases, Dengue fever, Buruli ulcer, or African trypanosomiaisis, however, lack safe, affordable good quality health products. The right to the highest attainable standard of health entitles people to access to good quality medicines[94]. R&D of health products is an essential component of improving and making medicines for neglected diseases available in the first place. Where no diagnostics, preventives, or treatments exist, States carry the responsibility to take reasonable measures to stimulate the medical innovation in order to ensure that much needed new products are developed and thereby become available[95].

This obligation arising from the right to the highest attainable standard of health is closely linked to the duties for States Parties in relation to the right to enjoy the benefits of scientific progress and its applications as enshrined in article 15 para. 1 (b) ICESCR[96]. In the past century, many essential discoveries in chemistry, molecular biology and biotechnology, such as the development of recombinant DNA or the sequencing of the human genome, have led to the advent of new technologies for drug discoveries and health techniques to diagnose, prevent and treat a variety of diseases[97]. These scientific developments, however, have rarely been applied to R&D for conditions prevalent in (L)DCs, or have not resulted into related product development (see chapter A. III. 4. (b)). Populations affected by neglected diseases are to a great extent deprived from the right to enjoy the benefits of scientific progress and its application.

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[93] Hunt, 2006, para. 51.

[94] Hunt, 2003, p. 8.

[95] *Ibid*., p. 13; CIPIH Report, 2006, p. 24.

[96] *Ibid*., p. 9; Hunt, 2007, p. 38.

[97] CIPIH Report, 2006, pp. 51, 52.

c) Domestic and international obligations of States under the right to the highest attainable standard of health

Parties have the obligation to combat discrimination, inequality and vulnerability[98]. In relation to the lack of adequate health technologies, it includes the promotion of the use of new scientific knowledge and techniques for R&D into neglected diseases affecting poor populations, as well as the facilitation of the transfer of the resulting benefits to endemic countries[99]. National authorities of endemic countries are the primary duty bearers of supporting R&D of health products to ensure their availability for the diagnosis, prevention and treatment of neglected diseases. The governments, mainly in the (L)DCs, are required to show that they are taking steps towards ensuring access to medicines, as well as availability of health products by promoting R&D into new medicines in a deliberate, concrete and targeted way, within their available resources[100].

Furthermore, according to the international responsibilities arising from the human rights provisions of international assistance and cooperation (article 2 para. 1 ICESCR), Parties in the position to assist are required to take actions that promote and protect the right to the highest attainable standard of health. This includes especially economic and technical assistance which enables (L)DCs to fulfill their core and other obligations[101]. This may involve a responsibility for industrialized countries to take positive measures to stimulate medical R&D into neglected diseases even though these diseases are not prevalent within their regions, in order to address the inequality in the field of global health R&D. Related interventions may include, for example, the development of a variety of economic, financial and commercial incentives in order to direct R&D towards (L)DCs health issues and compensate market failures. Support can be provided by direct funding of public research, or by allocating fi-

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[98] With regard to access to health products for populations affected by neglected diseases this means, for example, to create national medicine supply programs that are tailored to reach the vulnerable and disadvantaged populations.

[99] Hunt, 2007, p. 38; also Hunt, 2006, para. 47, 48.

[100] CESCR, General Comment No. 14, para. 30-33.

[101] *Ibid.*, para. 45.

nancial resources to R&D initiatives of the private sector and PDPs[102]. The responsibilities for international assistance may also involve the promotion of bilateral or multilateral international policies that are favorable to addressing the issue of neglected diseases. According to the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health this may, amongst others, include that States establish effective mechanisms within government that enhance coherence between health, human rights and trade. When formulating their trade policies, they should "take into account their national and international human rights obligations, including those related to the right to health", and to international assistance and cooperation[103].

3. Summary

The fundamental human right to the highest attainable standard of health encompasses the responsibility of States to take steps necessary for "the prevention, treatment and control of epidemic, endemic, occupational and other diseases" (article 12 para. 1 ICESCR) and for the development and diffusion of science (article 15 ICESCR). The monitoring body of the essential ICESCR, the CESCR, has developed an analytical framework to clarify the scope of obligations in relations to the right to the highest standard of health and its underlying concepts. The UN Special Rapporteur on the right to the highest attainable standard of health has further elaborated the principles and their applications on the issues of neglected diseases issues and access to medicines. Accordingly, States have the obligation to ensure that medicines are available, financially affordable, and physically accessible on the basis of non-discrimination to everyone within their jurisdiction. Industrialized countries in the position to assist also have a responsibility to take steps towards the full realization of the right to the highest attainable standard of health through international assistance and cooperation. While the opinions of both the

[102] Hunt, 2007, p. 38.

[103] Hunt, 2004, para. 79.

CESCR and the Special Rapporteur are not legally binding, they provide, nevertheless, authoritative guidance to clarify the meaning of the contents of the rights and obligations, and for States Parties a legal imperative to address the underlying health issues in (L)DCs[104]. Governments in both (L)DCs and industrialized countries can choose to follow the guidelines to promote R&D into neglected diseases[105].

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[104] Hunt 2003, p. 13; CIPIH Report, 2006, p. 22.

[105] Some literature and the international human rights community, however, increasingly considers the private pharmaceutical sector as accountable for ensuring the right to the highest attainable standards of health, based on its central societal role in developing and providing the essential tools for diagnosis, prevention and treatment of diseases. In general terms, the CESRC General Comment No. 14 acknowledged the responsibility of all members of society, including the private business sector, regarding the realization of the right to the highest attainable standard of health. The important role of the pharmaceutical companies in providing access to health products has also been recognized in the Millennium Development Goals (Goal eight, target 17), that calls on States to provide access to essential drugs available and affordable in (L)DCs in cooperation with pharmaceutical companies. Some literature has discussed a rights-sensitive approach of business entities and companies have developed self-reporting initiatives within their Corporate Social Responsibility strategies, as well as guidelines that explicitly affirm their human rights responsibilities in certain areas. Within his mandate, the Special Rapporteur on the right to health has developed "Human Rights Guidelines for the Pharmaceutical Companies in relation to Access to Medicines". While recognizing the complex market and social settings in which the companies operate and their responsibilities to enhance shareholder value, the Special Rapporteur, nevertheless, suggested a shared responsibility of the private sector to ensure the right to health. With respect to the lack of health products for neglected diseases, he called on pharmaceutical companies to provide some contribution to R&D in this field in terms of in-house R&D and/or the support of external initiatives; furthermore, he invited them to consult with other stakeholders, such as the WHO Special Programme for Research and Training in Tropical Diseases (TDR), and other relevant organizations, as well as to contribute constructively to initiatives that are searching for new approaches to accelerate R&D for neglected diseases. The Special Representative of the UN Secretary-General on the issue of human rights and transnational corporations noted that while not legally binding for business enterprises, human rights may, nevertheless, create implications for social norms and moral considerations for the private sector. *See* Hunt P., Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, 11 August 2008 (UN Doc. A/63/263), para. 23-25 *and* Ruggie J. G., Report of the Special Representative of the UN Secretary-General on the issue of human rights and transnational corporations and other business enterprises, 9 February 2007 (UN Doc. A/HCR/4/035). Furthermore, Leisinger K., On corporate responsibility and human rights, in Human security & business, 2006, pp. 1-40, available at http://www.novartisfoundation.org/platform/apps/Publication/getfmfile.asp?id=612&el=2412&se=9418807&doc=176&dse=5, accessed on 19 September 2009; UN Global Compact/Office of the United Nations High Commissioner for human Rights (UNHCHR), Embedding human rights in business practice, New York, November 2004; Novartis Corporate Citizenship Guideline 4 (Human Rights), available at

II. Millennium Development Goals

1. The United Nations Millennium Declaration and the Millennium Development Goals

In September 2000, the leaders of 189 countries adopted the UN Millennium Declaration (MD)[106] acknowledging the collective responsibility to uphold the principles of human dignity, equality and equity at the global level and, thus, reaffirmed their duty of international cooperation in solving international problems of an economic, social, cultural or humanitarian character, based on the principles of solidarity and shared responsibility (as provided in article 1 para. 3 of the UN Charter).

With more than one billion people currently living in conditions of extreme poverty, the development and poverty eradication are emphasized as key objectives of the international community, as well as the creation of an environment at the global and national levels which is conducive to achieve these major goals.

A number of commitments were made by both industrialized countries and (L)DCs on poverty reduction; good governance and the respect and fulfillment of human rights; the implementation of the target of providing ODA equal to 0.7 percent of gross national income and the grant of more generous development assistance, especially for those countries whose policies are effectively directed towards poverty reduction[107]; the adoption of fair trade rules to enhance access to developed markets for exports of the (L)DCs; the implementation of an enhanced program of debt relief, and on meeting the special needs for Africa, as well as access to new technologies and affordable essential medicines[108].

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http://www.corporatecitizenship.novartis.com/downloads/business-conduct/CC_guideline4_human_rights_en.pdf, accessed on 7 September 2009.

[106] UN General Assembly: UN Millennium Declaration adopted 18 September 2000 (UN Doc. GA 55/2).

[107] UN Millennium Declaration para. 15.

[108] United Nations: Road map towards the implementation of the Millennium Declaration, Report of the Secretary-General, 6 September 2001 (A/56/32), para. 136.

In order to materialize the vision of the Millennium Declaration, the Millennium Development Goals (MDGs) were developed as specific aims to be achieved by 2015: Goal 1 – Eradicate extreme poverty and hunger; Goal 2 – Achieve universal primary education; Goal 3 – Promote gender equality and empowerment of women; Goal 4 – Reduce child mortality by two-thirds; Goal 5 – Improve maternal health; Goal 6 – Combat HIV/AIDS, malaria, and other diseases; Goal 7 – ensure environmental sustainability; Goal 8 – Develop a global partnership for development.

Improved health of poor populations is central to the achievement of several MDGs and related targets demonstrating the understanding that the promotion of health, poverty eradication and the promotion of development are strongly linked. Three of the eight MDGs are health related (Goals 4, 5 and 6), including, furthermore, target 17 of Goal 8 to provide access to affordable essential drugs in (L)DCs in cooperation with pharmaceutical companies. Other MDGs involve important determinants of health[109] such as the eradication of extreme hunger (Goal 1, targets 8 and 9) and access to safe water (Goal 7, target 8). Gender equality is, furthermore, considered as important to promoting good health among children (Goal 3 – gender equity)[110].

The importance of improved health for the socio-economic development of individuals and countries has already been demonstrated by the WHO CMH in its report[111]. The key findings of the study presented evidence that countries with the weakest conditions of health and education have more difficulty in achieving sustained economic growth. The Commission suggested that each ten percent improvement of life expectancy could be associated with an increase in economic growth of about

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[109] Determinants of health include the social and economic environment, the physical environment and the person's individual characteristics and behavior. Influencing factors of the physical environment are, for example, safe water and clean air, healthy workplaces, safe houses, communities and roads, Employment and working conditions. *See* WHO, The determinants of health, available at http://www.who.int/hia/evidence/doh/en/index.html, accessed on 8 September 2009.

[110] Millennium Development Goals webpage, at http://www.un.org/millenniumgoals/, accessed on 7 September 2009.

[111] WHO CMH, 2001.

0.3 percent to 0.4 percent per year. An increased investment in global public goods, including multilateral policies, programs and initiatives that have a positive impact on health beyond a single country's border will be necessary in order to achieve an impact on the health of the poor populations. The report highlighted that investments should focus on R&D geared towards new medicines, vaccines and diagnostics to address the diseases affecting poor populations and countries. In addition, it recognized the need for complementary investments in other sectors, such as in education, water and sanitation that will have an impact on health as effective interventions to reduce poverty more effectively. Implementing the recommendations of the report, would save around eight million lives a year and generate economic benefits that present a six-fold return on the previous investments. As regards the R&D field the report recommended an increased funding through existing organizations focused on vaccine and drug development, such as the TDR, and the establishment of a new global health research fund for basic biomedical and health research with an annual funding of US $ 1.5 billion.

2. Neglected diseases in the Millennium Development Goals context

The commitment of the international community to the MDGs provides the fundament for policy frameworks for the promotion of an increased emphasis on better health in resource-poor countries. The UN Millennium Project Task Force on HIV/AIDS, malaria, tuberculosis, and access to essential medicines – Working Group on Access to Medicines underpinned improved access to medicines as a key component of strategies to strengthen health care[112]. Lack of medicines in most (L)DCs reflects both the lack of sufficient incentives for R&D of new affordable health products to target diseases that disproportionately affect (L)DCs, and the lack of affordability of and physical access to existing products. The inadequacy of the current incentive structure was seen as the main barrier to

[112] UN Millennium Project Task Force on HIV/AIDS, malaria, tuberculosis, and access to essential medicines – Working Group on Access to Medicines, Prescription for healthy development: increasing access to medicines, 2005, p.1.

the development of new and affordable pharmaceutical products for neglected diseases[113]. Addressing this issue requires a reorientation of medicinal research, better adjusted to the needs of poor populations, as well as new financing mechanism. The Task Force recommended activities such as greater cooperation between all sectors; substantially more financing from multiple sources; clear priorities for research efforts, also for the needs of the poor populations; and the effective management and technology and knowledge transfer. It highlighted expanded public investments in the medical research as particularly important to meet the priority health needs of the poor populations. "The international community should not rely on the research-based pharmaceutical industry to be the primary vehicle for developing medicines needed in (L)DCs", but should consider new ways of approaching innovation and pursue them with some urgency[114].

Goal 6 of the MDGs refers to the control of HIV/AIDS, malaria, tuberculosis and other diseases. Neglected diseases disproportionately or exclusively affecting poor populations in (L)DCs are included in these "other diseases". However, referring to the related targets and indicators formulated for Goal 6, the focus is on the three diseases HIV/AIDS malaria and tuberculosis, while official targets for the other diseases are not mentioned[115]. Accordingly, financial and political support has gone preferentially to the high-mortality illnesses[116]. In most cases, the UN publications on the MDGs also only include references to progresses achieved for the three major diseases[117].

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[113] *Ibid*., p. 6.

[114] *Ibid*., pp. 10 and 11.

[115] *See* UN Millennium Development Goals Indicators, at http://mdgs.un.org/unsd/mdg/Host.aspx?Content=Indicators/OfficialList.htm, accessed on 15 September 2009.

[116] *See* also chapter A. II. 2.

[117] For example, the UN Millennium Development Goals Report 2008 and 2007. Available at http://www.un.org/millenniumgoals/pdf/The%20Millennium%20Development%20Goals%20Report%202008.pdf and http://www.un.org/millenniumgoals/pdf/mdg2007.pdf, accessed on 17 September 2009.

Currently, only a small percentage of the global funding for health R&D is dedicated to the creation of new technologies for diseases of the (L)DCs. Development of new diagnosis, prevention and treatment tools for neglected diseases, however, can contribute to achieve the MDGs, and to reduce poverty, child mortality and improve maternal health. Beyond mortality figures, neglected diseases are cause of serious and permanent disabilities and deformities affecting about one billion people worldwide and responsible for the most severe health-related impairments of social and economic activities, particularly within the poorest populations in (L)DCs[118]. They are indicators of poverty concentrating in remote rural regions or conflict zones in conditions of poverty.

According to the WHO, the neglected diseases control represents a largely untapped development opportunity for addressing poverty in the (L)DCs as key objective of the MDGs, thus directly impacting their achievement[119]. The Organization promotes the value and cost-effectiveness of neglected diseases control as a "pro-poor" strategy. A number of neglected diseases, such as lymphatic filariasis or schistosomiasis, can be controlled by low-cost (often donated), safe, effective and easy to administer health products. Furthermore, experiences with control strategies for these neglected diseases, a high return on investments and a solid track record of success provide evidence for potential added value to the control of the three other diseases HIV/AIDS, malaria and tuberculosis[120]. Initiatives to achieve the MDGs require priori-

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[118] WHO, Goal 6: Communicable diseases prevention and control. Available at http://www.who.int/mdg/goals/goal6/communicable_disease_prevention/en/index.html, accessed on 8 September 2009 [hereinafter WHO, Goal 6].

[119] WHO, Integrated control of the neglected tropical diseases – A neglected opportunity ripe for action, Joint paper by the WHO and the Carter Center presented to the Global Health and the United Nations meeting, May 2008 (WHO/HTM/NDT/2008.1); also WHO, Goal 6: Communicable diseases prevention and control, available at http://www.who.int/mdg/goals/goal6/communicable_disease_prevention/en/index.html, accessed on 8 September 2009.

[120] *Ibid*.; *see* also Lammie P.J., Fenwick A., Utzinger J., A blueprint for success: integration of neglected tropical diseases control programmes, Trends Parasitol. 22, 2006, pp. 313-321; Molyneux D.H., Hotez P.J., Fenwick A., 2005, Rapid impact interventions: How a policy of integrated control for Africa's neglected tropical diseases could benefit the poor, PLoS Med. 2, e336.

tizing intensified control of neglected diseases as a direct contribution to MDG Goal 6 to reduce communicable diseases in (L)DCs, and as an indirect effort to reduce poverty (Goal 1)[121]. For neglected diseases without adequate health technologies the current control strategy involves early detection approaches, and requires skilled personnel, as well as costly and complicated treatments, including hospitalization and surgery. The need for innovative, simple, safe and cost-effective health products is obvious and would tremendously impact the existing control strategy. The WHO proposes options for actions that include, amongst others, to raise the profile of the neglected diseases on the development agenda in order to increase awareness and promote political commitment on forums such as the G8 meetings and the MDG summits. Furthermore, it includes the promotion of partnerships (reflecting MDG Goal 8) for the control of neglected diseases across various sectors, including industry, academic or advocacy groups, in order to join different resources and perspectives[122].

Various global estimates of necessary investments to achieve the MDGs have been provided; they range from US $ 20 billion to US $ 70 billion a year[123]. According to the Organization for Economic Co-Operation and Development (OECD), the current ODA funding of the 22 member countries comprised in the list of the Development Assistance Committee (DAC) of OECD, accounts for almost US $ 120 billion in the year 2008[124]. Among the DAC members, five met the 0.7 percent commitment in 2008[125].

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[121] *Ibid*.

[122] WHO, Integrated control of the neglected tropical diseases – A neglected opportunity ripe for action, Joint paper by the WHO and the Carter Center presented to the Global Health and the United Nations meeting, May 2008 ((WHO/HTM/NDT/2008.1), p. iii.

[123] *See*, for example, Wagstaff A., Claeson M., The Millennium Development Goals for Health: Rising to the challenges, World Bank Washington D.C., 2004, pp. 1-186; WHO CMH, 2001.

[124] OECD, Net Official Development Assistance in 2008, 30 March 2009. Available at http://www.oecd.org/dataoecd/48/34/42459170.pdf, accessed on 16 September 2009.

[125] Denmark, Netherlands, Luxembourg, Norway, Sweden. *Ibid*.

Substantially increased ODA spending will be required to accelerate the progress toward the MDGs. This includes an increase in the proportion of health ODA funding devoted, including, amongst others, health R&D and research capacity strengthening.

The lack of health products may not be the primary hindrance for faster advancement towards the achievement of the MDGs; new health technologies that can be delivered by resource-limited health systems in (L)DCs, nevertheless, could greatly improve the progress.

III. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the Doha Ministerial Declaration

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)[126], negotiated during the Uruguay Round of multilateral trade negotiations of the General Agreement on Tariffs and Trade (GATT), came into force in 1995. The GATT process led to the adoption of an Agreement Establishing the World Trade Organization (WTO). Many industrialized countries and (L)DCs have joined the WTO[127]. The TRIPS Agreement is an integral part of the WTO Agreement. It is binding on all WTO Member States and is legally enforceable through the WTO dispute settlement procedure and sanctions withdrawing WTO advantages.

TRIPS establishes a global minimum protection standard for the principal intellectual property rights (IPRs), amongst others, patents, and provides provisions for their enforcement. It includes specific provisions on the coverage[128] and criteria of patentability, although not defining

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[126] WTO Agreement on Trade-related Aspects of Intellectual Property Rights. Text available at http://www.wto.org/english/tratop_e/trips_e/t_agm0_e.htm, accessed on 9 September 2009.

[127] As of July 2008, the WTO had 153 Member States. *See* WTO, Members and States, at http://www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm, accessed on 8 September 2009.

[128] Article 1 para. 1 TRIPS: "Members should give effect to the provisions of this Agreement. Members may, but shall not be obliged to, implement in their law more extensive protection than is required by this Agreement, provided that such protection does not contravene the

them[129], and the minimum protection period of 20 years[130]. The comprehensive rules on the protection of the IPRs are subject to international legal interpretation and enforcement through an effective dispute settlement mechanism[131].

Various provisions of the TRIPS Agreement may have substantial impact on public health related issues, such as R&D for and access to medicines, as described below. Some have been reason for further negotiations and clarification between Member States.

1. Objectives and principles of TRIPS with health relevance

The main objective of the TRIPS Agreement is the promotion of technological innovation and transfer and dissemination of technology through the protection and enforcement of IPRs, in a manner conducive to social and economic welfare, and to a balance of rights and obligations (article 7). Patents, as IPRs intend to stimulate innovation by conferring the right owner with an exclusivity right for the exploitation of the protected invention to recover investments in R&D and make a profit. As discussed above (chapter A.II.3 b)), patent protection is viewed as an indispensable prerequisite for R&D in the pharmaceutical sector[132]. This incentivizing

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provisions of this Agreement. Members shall be free to determine the appropriate method of implementing the provisions of this Agreement within their won legal system and practice".

Since the provision does not define the criteria for patentability, Member States are free to consider their own definition and interpretation of the subject matters.

[129] Article 27 para. 1 TRIPS: "Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or process, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. […]."

[130] Article 33 TRIPS.

[131] Article 64 TRIPS.

[132] The high dependency of the pharmaceutical sector on the patent systems has been demonstrated by various studies, amongst others, Levin R.D., Klevorick A.V., Nelson R.R., Winter S.G., Appropriating the returns from industrial R&D, Brookings Papers on Economic Activity 3, 1987, pp. 783-820; Cohen W., Nelson R.R., Walsh J.P., Protecting their intellectual assets: Appropriability conditions and why U.S. manufacturing firms patent (or not), Working paper No. 7552, National Bureau of Economic Research. 2002, pp. 1-31; Reinhardt U.E., The pharmaceutical sector in health care, in Pharmaceutical innovation: Incentives, competition

role, however, is contested by some stakeholders, as far as patents may impede the innovation they are intended to promote, such as in the case of upstream scientific outcomes, research tools, or overly broad claims in patent applications that hamper follow-on research[133].

A Swiss study identified areas where patents cause access problems to certain technologies, including, for example, the field of genetic or diagnostic testing[134]. The criteria of patentability and the quality of the patent examination can also create barriers to fostering innovation[135]. Considering these aspects, the Swiss study noted: "Good intellectual property policy is not necessarily equivalent to long-lasting and broadly scoped intellectual property rights. The policy objective should therefore be good policy, not maximal rights. High quality patents fully satisfy the patenting criteria; they provide sufficient disclosure and are guaranteed to be valid. Poor patent quality can lead to reduction in investment and commercialization of innovation. It can slow progress in cumulative technologies and increase the level of right fragmentation. [...] The cor-

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and cost-benefit analysis in international perspective, eds. Sloan F.A. ad Hsieh C.-R., New York, Cambridge University Press, 2007, pp. 25 ff.

[133] National Research Council, Reaping the benefits of genomic and proteomic research intellectual property rights, innovation and public health, Washington, DC, The National Academic Press, 2006, available at http://www.nap.edu/openbook.php?isbn=0309100674, accessed on 13 September 2009; Cho M.K., Illangasekare S., Weaver M.A., Leonard D.G.B., Merz J.F., Effects of patents and licenses on the provision of clinical genetic testing services, Journal of Molecular Diagnostics, 2003, Vol. 5, pp. 3-8; Rimmer M., Myriad Genetics: Patent law and genetic testing, European Intellectual Property Review, 20, 2003, pp. 21-23; CIPIH Report, 2006, pp. 64 ff.

[134] In order to counteract abusive monopoly positions, a clinical use exemption and offering clinical laboratories non-exclusive licenses for a patented genetic test on reasonable terms were seen as efficient remedies, as were compulsory licensing conditions to ensure access to technology. With respect to the patenting of DNA, the study proposes the limitation of patent protection to concrete disclosure functions of the DNA in order to increase access to genetic inventions. *See* Thumm N., Research and patenting in biotechnology – A survey in Switzerland, Swiss Federal Institute of Intellectual Property, Publication No. 1 (12.03), 2003, pp. 54 ff and chapter 10 – summary – no. 17-19 and 23, and Conclusions No. X and XI. *See* also Kraus D., Les conditions pour une protection équilibrée de la propriété intellectuelle en Suisse, La Vie économique / Die Volkswirtschaft 7-8 / 2006, pp. 4-8.

[135] US Federal Trade Commission, To promote innovation: The proper balance of competition and patent law policy, 2003, Executive Summary, p. 3.

rect application of patentability criteria would help to increase the quality of patents."

Article 7 TRIPS further requires Member States to implement the Agreement obligations in a way that considers the objective of transfer and dissemination of technology. Depending on the development stage of a country, transfer of technology may include a variety of activities, such as the acquisition of physical objects and equipment, imitation through reverse engineering, formal agreements and licenses, foreign direct investments, development cooperation activities such as technical assistance and trainings, and other means[136].

This objective is also addressed in article 66 para. 2 TRIPS, which obliges industrialized country Members to provide incentives to enterprises and institutions in their territories for the purpose of promoting and encouraging technology transfer to (L)DCs in order to enable them to create a sound and viable technological base[137].

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[136] Correa C., Can the TRIPS Agreement foster technology transfer to developing countries?, in International public goods and transfer of technology under a globalized intellectual property regime, eds. By Maskus K. E. and Reichman J. H., Cambridge University Press, 2005, p. 229.

[137] The development of the nature of the duties included in both articles (7 and 66 para. 2), as well as the examination of relationship between trade, IPR protection and technology transfer is part of the responsibilities of the Working Group on Trade and Technology Transfer in the WTO. The Working Group aims, amongst others, to establish recommendations of steps that might be taken within the mandate of the WTO to increase flows of technology to (L)DCs. In 2003, the Council for TRIPS adopted a Decision on the Implementation of article 66 para. 2 TRIPS, which set up mechanisms for ensuring the monitoring and full implementation of the obligations under article 66 para. 2, including the submission of annual reports on actions taken or planned.

The Members have to provide, amongst others, an overview of the incentives regime put in place to fulfill the obligations of article 66 para. 2 TRIPS, including any specific legislative, policy and regulatory framework; information on eligible enterprises and other institutions; any information available on the functioning in practice of these incentives (for example, statistical information on the use of the incentives by the eligible entity; the type of technology that has been transferred by these entities, and the terms on which it has been transformed; the mode of technology transfer).

See WTO, Decision of the Council for TRIPS on the Implementation of Article 66.2 of the TRIPS Agreement, of 19 February 2003 (IP/C/28). Available at http://www.wto.int/english/tratop_e/trips_e/techtransfer_e.htm, accessed on 13 September 2009.

Regarding the pharmaceutical sector, the WTO General Council Decision of 6 December 2005, amending the TRIPS Agreement[138], recognized the desirability of promoting the transfer of technology and capacity building in this area in countries without sufficient or no related structure. Members stated to use the TRIPS system in a way which would promote this objective and to pay special attention to the transfer of technology and capacity building in the pharmaceutical sector in the work to be undertaken pursuant to the duties included under articles 66 para. 2 and 7 TRIPS. One according initiative is the joint program of the German Government, in association with the United Nations Conference on Trade and Development (UNCTAD), the United Nations Industrial Development Organization (UNIDO), and the United Kingdom Department for International Development (DFID) with the goal to assist selected (L)DCs in the establishment of local capacities for pharmaceutical production[139].

IPRs should, finally, work in a manner conducive to social and economic welfare (article 7 TRIPS). Accordingly, the recognition and enforcement of IPRs are subject to higher social values as further elaborated in article 8 TRIPS[140], to which, some literature includes international human

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In 2005, Swiss activities related to the implementation of article 66 para. 2 TRIPS included, amongst others, the support of private-sector investments in (L)DCs (for example the support of small and medium-sized enterprises (SME) trough private equity funds investments in (L)DCs or grants to the African Project Development Facility); the support of commercial establishment of (L)DCs companies in Switzerland and other industrialized countries; training activities for personnel from (L)DCs; the support of research activities of the Swiss Tropical Institute and other Swiss institutions that provide advice and assistance to WHO for its "Roll-Back Malaria" program; assistance in preparing and enforcing laws on the protection of IPRs. *See* WTO Council for TRIPS, Report on the implementation of Article 66.2 of the TRIPS Agreement, Switzerland, 6 October 2005 (IP/C/W/452/Add.1).

138 WTO General Council Decision, Amendment to the TRIPS Agreement of December 6, 2005 (WT/L 641) (with Annex setting out Article 31 *bis* TRIPS), para. 6 of the Annex setting out article 31 *bis* TRIPS. Available at http://www.wto.org/english/tratop_e/trips_e/wtl641_e.htm, accessed on 10 September 2009.

139 Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) GmbH, The viability of pharmaceutical manufacturing in Ghana to address priority endemic diseases in the West Africa sub-region, 2007, p. 5.

140 Correa C., Trade related Aspects of Intellectual Property Rights, A commentary on the TRIPS Agreement, Oxford University Press, 2007, p. 99.

rights[141]. In a detailed survey of the relationship between trade and human rights, the High Commissioner for Human Rights analyzed the effects of various fields enclosed in the WTO framework, including the TRIPS Agreement, on the human rights situation in WTO Member States[142]. The role of liberalization of international trade for economic development and generation of resources to the full realization of the economic, social and cultural human rights is undisputed. The reports, however, found that trade liberalization can negatively impact the enjoyment of human rights, particularly the economic, social and cultural rights of the ICESCR. The High Commissioner concludes that it is the primary responsibility of States to protect human rights and pursue human rights principles. Due to the challenges resulting from globalization, governments need to ensure that trade be liberalized in a manner that is in harmony with their obligations to respect, protect and implement human rights.

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[141] One prevailing question here is, if and how far human rights doctrines have to be considered by WTO panels or the Appellate Body in legal disputes related to the WTO Agreements. This issue is part of ongoing international debate. It is, however, not subject of the underlying study. *See* Marceau G., WTO dispute settlement and human rights, European Journal of International La 13 (4), 2002, pp. 753-814; Pauwelyn J., Human rights in WTO Dispute settlements, in Cottier T., Pauwelyn J., and Burgi Bonanomi E., Human rights and international trade, Oxford University Press, 2005, pp. 205-231; Petersmann E.-U., Time for a United Nations 'Global Compact' for Integrating Human Rights into the Law of Worldwide Organizations: Lessons from European Integration, in: European Journal of International Law 13 (2002) pp. 621-650; Petersmann E.-U., The Human Rights Approach to International Trade Advocated by the UN High Commissioner for Human Rights and by the ILO: Is it Relevant for WTO Law and Policy? in: E.U.Petersmann (ed), 'Preparing the Doha Development Round: Challenges to the Legitimacy and Efficiency of the World Trading System', EUI 2004, pp. 1-27, and pp. 29-56; Petersmann E.-U., Human Rights, Constitutionalism and the WTO: Challenges for WTO Jurisprudence and Civil Society, in: Leiden Journal of International Law 19 (2006), pp. 633-667.

[142] UN ECOSOC, Economic, Social and Cultural Rights: The impact of the Agreement on Trade-related Aspects of Intellectual Property rights. Report of the High Commissioner, 27 June 2001 (E/CN.4/Sub.2/13) [hereinafter High Commissioner on TRIPS, 2001]; further, UN ECOSOC, Economic, Social and Cultural Rights: Globalization and its impact on the full enjoyment of human rights, Report of the High Commissioner for Human Rights submitted in accordance with Commission on Human Rights resolution 2001/32, 15 January 2002 (E/CN.4/2002/54); UN ECOSOC, Economic, Social and Cultural Rights: Liberalization of trade in services and human rights, Report of the High Commissioner for Human Rights, 25 June 2002 (E/CN.4/2002/9).

With respect to intellectual property, this requires to strike a balance between the public and private interests found under article 15 ICESCR, namely the right of everyone to take part in cultural life and to enjoy the benefits of scientific progress and its application (article 15 para.1 a) and b) ICESCR) and the right of everyone to benefit from the protection of the moral interests resulting from any scientific, literary or artistic production of which he or she is the author (article 15 c) ICESCR). A human rights approach requires finding the balance based on the primary objective of promoting and protecting human rights, and in a way not detrimental to any of the other rights contained in the ICESCR[143]. Links between human rights and the TRIPS Agreement exist through article 7 TRIPS that recognizes as objective a need to balance between rights and obligations, and between the interests of producers and users of technological knowledge with the wider objective of promoting social and economic welfare[144]. TRIPS offers various provisions to achieve the balance, for example the right of Members to implement measures to protect public health and nutrition (article 8, 31, 31 *bis* TRIPS); to protect the environment (article 27 para. 2 TRIPS); to encourage technology transfer (amongst others articles 7, 66 para. 2 TRIPS); for the advancement of socio-economic development (article 8 para. 1 TRIPS); and for the promotion of fairness (article 8 para. 2 and 40 TRIPS) and international cooperation (article 66 para. 2 and 67). These measures indicate a certain degree of coherence with the balance sought under article 15 ICESCR in the promotion of the right to food[145] and to the highest attainable standard of health[146], and the right to development[147] and the right to enjoy the benefits of scientific progress[148]. Despite these various links to human rights, TRIPS has a fundamental different approach. Its overall goal is the promotion of innovation through the provision of commercial incen-

[143] High Commissioner on TRIPS, 2001, para. 10-13.

[144] *Ibid*., para. 16.

[145] Article 11 para. 1 ICESCR.

[146] Article 12 ICESCR.

[147] Article 55 (a) UN Charter.

[148] Article 15 para. 1 b) ICESCR.

tives and their protection. The links with the subject matters of human rights are generally expressed in terms of exceptions to the rule rather than the guiding principles themselves, and are additionally made subject to the provisions of the Agreement. In contrast, a human rights approach would consider the promotion of and protection of the economic, social and cultural human rights of the ICECR as core element[149]. While recognizing that the protection of commercial objectives is not necessarily incompatible with the promotion of human rights, the High Commissioner concludes that it still much depends on how the TRIPS Agreement is actually implemented. TRIPS recognizes significant operational flexibilities that can be used in ways that would be fully compatible with the promotion and protection of human rights[150]. In conclusion, Members should consider, amongst others, an implementation and application of TRIPS that contribute to the achievement of the balance between the interests of the general public and those of the inventors, including the establishment of standards of patentability for pharmaceuticals in consideration of their implications for health and the use of the flexibilities provided in TRIPS to promote access to medicines[151].

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[149] High Commissioner on TRIPS, 2001, para. 22. The High Commissioner considers further differences between the human rights approach and the ultimate goal of TRIPS. This includes, amongst others, the focus of TRIPS on protection forms that have been developed in industrialized countries. Patents, for example, are most relevant for the protection of modern forms of technology, such as biotechnology. As such they are most important for the innovation situation in industrialized countries, as also reflected in the statistics of patent applications that demonstrate the predominance of technology holders and applicants in the developed regions (para. 2). Furthermore, while identifying the need to balance various interests, the TRIPS Agreement does not further set out in greater details the content of these responsibilities. In contrast to this, the minimum standard for the protection and enforcement of the IPRs are well established, showing that the balance identified in TRIPS might not equate the balance required under article 15 ICESCR (para. 23).

[150] *Ibid*., para. 22 and 28.

[151] *Ibid*., para. 61, 63, 66.

2. TRIPS flexibilities and access to pharmaceutical products

Members may adopt measures that are necessary to protect, amongst others, public health, provided that such measures are consistent with the provisions of the TRIPS Agreement (article 8 para. 1 TRIPS).

Both articles, 7 and 8 para. 1, are central for the national implementation and the interpretation of the TRIPS Agreement. This has been confirmed in the Ministerial Declaration adopted at the Doha WTO Ministerial Conference in 2001[152] and the Declaration on the TRIPS Agreement and Public Health of November 2001[153]. These instruments marked an international consensus on the interpretation and implementation of TRIPS, in the light of supporting public health, by promoting access to medicines and the creation of new medicines. Member States recognized the importance of intellectual property protection for the development of new medicines[154]. However, they affirmed that the TRIPS Agreement does not and should not prevent members from taking measures to protect public health, and that it can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health[155]. This referred particularly to the flexibilities included in the TRIPS Agreement related to the conditions for the issue of compulsory licenses by governments to ensure access to patented pharmaceuticals of need[156].

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[152] Ministerial Declaration, WTO Forth Ministerial Conference, Doha, 20 November 2001 (WTO/MIN(01)/DEC/1), para. 19. Available at http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_e.pdf, accessed on 10 September 2001.

[153] Declaration on the TRIPS Agreement and Public Health, WTO Fourth Ministerial Conference, Doha, 20 November 2001 (WT/MIN(01)/DEC/2). Available at http://www.wto.org/english/theWTO_e/minist_e/min01_e/mindecl_trips_e.htm, accessed on 10 September 2009 [hereinafter Declaration on the TRIPS Agreement and Public Health].

Paragraph 5 (a) of the Declaration states: "In applying the customary rules of interpretation of public international law, each provision of the TRIPS Agreement shall be read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles."

[154] *Ibid*., para. 3.

[155] *Ibid*., para. 4.

[156] Compulsory licensing enables a government to license the use of an invention to a third party or agency without the consent of the patent holder. The patent owner retains its rights and has to be paid adequate remuneration according to the circumstances of the case (Article 31 TRIPS). In the pharmaceutical sector compulsory licenses have been issued, amongst oth-

Most countries implemented a provision for compulsory licenses into their national legislation. Grounds for compulsory licensing include national emergency or other circumstances of extreme urgency or cases of public non-commercial use. Member States are free to determine what constitutes the reasons for compulsory licensing and may include public health crisis such as those relating to HIV/AIDS, tuberculosis, malaria and other epidemics[157].

Originally, compulsory licensing was deemed to be used predominately for the supply of the domestic market (article 31 (f) TRIPS). This provision, however, limited (L)DCs which lack domestic manufacturing capacities to benefit from access to inexpensive generic medical products. To address this issue, the WTO adopted a temporary solution, the "Decision on the Implementation of Paragraph 6 of the Doha Declaration on TRIPS Agreement and Public Health" (August 30, 2003)[158]. It allows countries with local manufacturing capacity to issue compulsory licenses to produce and export medicines to countries without adequate manufacturing capacity, under the conditions set out in the Decision, thus enabling (L)DCs to access alternative supplies of medicines in the event of a public health crisis. For effective operation of the system, potential importing and exporting countries need to change their national patent laws accordingly[159]. With the Decision of December 6, 2005[160], this procedure is supposed to be implemented permanently into the TRIPS Agreement (article 31 *bis* TRIPS).

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ers, to promote the availability of needed medicines. *See* also Kraus D., Compulsory licenses for the exportation of generic versions of patented pharmaceutical products, ATDF Journal Vol. 3 Issue 1, March 2006, pp. 38-40.

[157] Declaration on the TRIPS Agreement and Public Health, para. 5 c.

[158] WTO, Decision of the General Council of 30 August 2003, Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health (WT/L/540), September 2003. Available at http://www.wto.org/english/tratop_E/TRIPS_e/implem_para6_e.htm, accessed on 13 September 2009.

[159] For example, Canada, India, Norway, or Switzerland have implemented the Decision as potential export countries.

[160] WTO General Council Decision, Amendment to the TRIPS Agreement of December 6, 2005 (WT/L 641). Available at http://www.wto.org/english/tratop_e/trips_e/wtl641_e.htm, accessed on 10 September 2009.

As to date this procedure[161] has been used in one case. In 2007, Canada issued a compulsory license for the manufacturing and export of a HIV/AIDS medicine to Rwanda. The authorization for the generic production followed the notification of Rwanda to the WTO about the intention to import a certain quantity of the drug from Canada. The country's intellectual property office authorized a large generic producer to manufacture the required supply[162].

Access to medicines in (L)DCs is a crucial public health issue and has been addressed by the "safeguards" implemented in the TRIPS Agreement and further clarified by the subsequent WTO Declarations. Compulsory licenses have been issued for certain drugs in various countries. The threat to issue a compulsory license has helped countries to negotiate better supply prices with the patent holders[163].

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[161] The procedure for Article 31 *bis* TRIPS is described in Paragraph 2 of the Annex to the TRIPS Agreement. It requires, amongst others, the importing country to notify about the needed products and the expected quantities, and the grant of a compulsory license in the export country after the request of a voluntary license to the patent owner (as described in Article 31 (b)), or the invocation of a health emergency in a foreign country. The compulsory license must be granted only to produce and export the amount necessary to meet the needs of the importing country. The supplier is required to label the products to be supplied under the Decision to allow their clear identification and avoid diversion to other markets; furthermore, measures should be provided to distinguish the generic product from the branded one, for example, in packaging, coloring and shaping. The supplier must post on a website certain information about the generic product. The exporting country must make a notification of the grant of the license to the Council of TRIPS. *See* Amendment to the TRIPS Agreement, of December 6, 2005 (WT/L 641), Annex to the TRIPS Agreement.

[162] Canadian Intellectual Property Office, Commissioner of Patents authorizes the manufacture of an anti-viral drug to Rwanda, September 19, 2007. Available at http://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/wr01236.html, accessed on 10 September 2009; Notification under paragraph 2 (c) of the Decision of 30 August 2003 on the implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, Canada, 4 October 2007 (IP/N/10/CAN/1), available at http://www.wto.org/english/tratop_e/trips_e/public_health_notif_export_e.htm, accessed on 10 September 2009; Notification under paragraph 2 (a) of the Decision of August 30, 2003 on the implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, Rwanda, 19 July 2007 (IP/N/RWA/1), available at http://www.wto.org/english/tratop_e/trips_e/public_health_notif_import_e.htm, accessed on 10 September 2009.

[163] For example, in 2007, the Brazilian Government granted a compulsory license for an antiretroviral for public use of Merck's Brazilian patent on Efavirenz. The drug is used to treat approximately 75.000 of 200.000 patients under treatment in Brazil. With the introduction of generic versions of the medicines the Brazilian Government estimated a cost-saving of an-

The access to medicines issue, however, is mainly discussed in relation to pandemics such as HIV/AIDS. Existing products for some neglected diseases, as defined in this study, have so far not been subject to the questions of compulsory licensing. Some of the required health products to treat the infectious conditions are donated by the pharmaceutical companies showing some preparedness of the commercial entities to contribute to the control of the diseases in endemic regions. The compulsory license related provisions, however, may be applicable in the case that a (L)DC determines the prevalence of a neglected disease as public health crisis. The articles 31 and 31 *bis* TRIPS may provide instruments for (L)DC countries to negotiate affordable prices for required neglected diseases medicines or to ensure access to them.

3. TRIPS provisions with relevance for pharmaceutical R&D

a) Patentability requirements, article 27 TRIPS

Standards for patentability also have a potential effect on health and R&D. Depending on their definition in national laws, their determined scope and their application, the criteria for issuing a patent can support or inhibit medical and pharmaceutical R&D.

Patents for pharmaceutical innovation may be granted for new chemical entities. However, in many cases, intellectual property protection is rather provided for new uses of a drug, processes, dosage forms, formulations and different forms of the same molecule, including patents on genes and genomic sequences. The patentability of the latter examples strongly depends on the definition of the novelty and inventive step criteria in national legislations and practices. Some countries took the approach of limiting patent protection where no new product was developed, having public health concerns in mind. The 2005 Indian patent leg-

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nual US $ 30 million. *See* Cohen J., Brazil, Thailand override big pharma patents, Science Magazine, 11 May 2007, p. 816. Before the issue of this compulsory license Brazil had managed to negotiate settlements with the foreign suppliers. *See* Abbott F.A., Reichman J.H., The Doha round's public health legacy: Strategies for the production and diffusion of patented medicines under the amended TRIPS provisions, Journal of International Economic Law 10 (4), pp. 950 ff.

islation, for example, excludes from patentability inventions that are "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance, the mere discovery of any new property or new use of a known substance, or the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant" (Section 3 (d))[164]. It remains to be seen how this rule will be interpreted and applied by the Indian patent office and Indian courts in the future. A different approach, for example, is employed at the European Patent Office (EPO). The revised European Patent Convention (EPC) of 13 December 2000 explicitly acknowledges the patentability of any substance or composition for *any specific use* in a medical method provided that such use is not comprised in the state of the art (new article 54 para. 5). The revision enshrined case law evolved by the EPO Enlarged Board of Appeal that allowed the patentability of so-called "second medical indications" of pharmaceutical products. This refers to the new use of the patented product, i.e. for a different treatment than the one already known[165].

A practice of granting broad patents can result in undue restrictions on biomedical research. This includes particularly patents for innovations at the early stage of research that can be used to control and hinder life-

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[164] Patents (Amendment) Act, 2005. Available at http://www.patentoffice.nic.in/ipr/patent/patent_2005.pdf, accessed on 8 September 2009.

[165] The "second medical use" doctrine was not included in the EPC (1973), but was developed through case law. The Enlarged Board of Appeal of the EPO decided that patents were to be granted for a second medical indication for a known pharmaceutical under the so-called "Swiss-type-claim" (i.e. directed at the *use of substance X (or composition comprising X) for the manufacture of a medicament for treating disease Y*). Under this Swiss formulation, claims in patent applications are not excluded from patentability if they are directed to the use of a substance or composition for the manufacture of a medicament for a specified new and innovative therapeutic application. This is applicable even in a case in which the process of manufacture as such does not differ from known processes using the same active ingredient.

See EPO Decision of the Enlarged Board of Appeal, *"Interpretation of the EPC/ Vienna Convention" – "Therapeutical use claiming"* G 1-6/83, OJ EPO 1995, p. 64, available at http://documents.epo.org/projects/babylon/eponet.nsf/0/5891FCEDA0C96A07C12572C8006C5110/$File/g830001.pdf, accessed on 19 September 2009; and Legal Advice from the Swiss Federal Intellectual Property Office, OJ EPO 1985, 91.

saving innovation that depends on the first invention[166]. Further, depending on their application, the standards for the grant of patents can contribute to "ever-greening" – a process that refers to the patenting of minor innovations to effectively extend the life of existing patents beyond the term of 20 years. This protection extension can also inhibit research efforts.

b) Exceptions to the rights conferred by a patent, article 30 TRIPS

The Members of TRIPS may provide limited exceptions to the exclusivity rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking into account of the legitimate interests of third parties (article 30 TRIPS).

Experimental use of the patented invention and the so-called "Bolar" or "early working" exception are internationally accepted exceptions. Both options provide governments with the opportunity for research supporting policy setting.

The experimental use exception on patented inventions may include the use of a patented invention for research experimentation and teaching purposes. It can create a research fostering environment, allowing others, for example, to invent around the patented innovation and undertake improvement activities, including the use of the patented substance for clinical trial phases, irrespective of an eventual commercial objective. In consideration of the pharmaceutical and medical field, a broad rule allowing experimental use of patented innovation can help foster follow-on health related research and innovation, including new health products for neglected diseases. Patent legislations in most European countries generally allow both private, non-commercial research acts and experimental use related to the subject matter of the patented invention,

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[166] Heller M.A., Eisenberg R.S., Can patents deter innovation? The anticommons in biomedical research, Science 1 May 1998, Vol. 280, pp. 698-701. Available at http://www.sciencemag.org/cgi/content/full/280/5364/698, accessed on 14 September 2009.

even for commercial purposes[167]. In Switzerland, for example, the revised Patent Act of 2008 includes a broad research exemption that permits private use, as well as acts for the purpose of research experimentation, which serve to gain insight about the object of an invention including its possible utilities; any scientific research on the object of the invention is allowed (article 9 par. 1 lit. b Swiss Patent Law)[168]. Additionally, the revised Patent Act further provide a non-exclusive license to research tool patents, however, with the obligation to pay license fees to the patent holder (article 40 lit. b Swiss Patent Law).

A further exception under article 30 TRIPS is the so-called "Bolar" or "early-working" exception. It allows the use of a patented pharmaceutical invention to perform tests and obtain the market approval from the regulatory authority, before the expiry of the patent[169]. The producer can then market the generic version immediately after the patent expiry. Similar exceptions have been established in legislations in numerous countries[170]. It allows and promotes generic competition within the

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[167] These regulations have been inspired by the Community Patent Convention (1975), article 27 (b) that states that acts done for experimental purposes relating to the subject-matter of the patented invention are exempted from liability for patent infringement. The Community Patent Convention has not come into force, but has been ratified by some European countries, such as the United Kingdom and Germany.

[168] *See* Federal Law on Patents for Inventions of 25 June 1954 (Status as on 1 July 2008) (232.14), in German available at http://www.admin.ch/ch/d/sr/2/232.14.de.pdf, accessed on 14 September 2009.

[169] The exception is named after the US case *Roche Products Inc vs. Bolar Pharmaceutical Co.* (733 F 2d 858, Fed. Cir., 04/23/1984). The court rejected Bolar's contention holding that the use of a patented substance in chemical tests before patent expiry for the purpose to achieve FDA approval would constitute a legitimate use under the experimental use exception to the patent law.

[170] For example, in Switzerland, article 9 para. c) of the Patent Act regulates that the effects of a patent do not extent to acts necessary to obtain a marketing authorization for a medicine according to the provision of the law of 15 December 2000 on therapeutic products.

The legislations in European Union (EU) Member States are based on the implementation of Article 10 (b) of the Directive 2004/27/EC. The regulation provides for an exemption from patent infringement regarding "the necessary studies and trials and the consequential practical requirements" carried out in order to obtain regulatory approval for medical products for the EU, including experiments and trials (preclinical and clinical) in order to obtain regulatory approval for a generic (Article 10 para.2 b)), a quasi generic (Article 10 para.3) or a biosimilar (Article 10 para. 4). *See* Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relat-

pharmaceutical sector and as such fosters access to medicines for consumers. A WTO Dispute Settlement Panel upheld such an exception implemented by Canada as permissible under article 30 TRIPS[171].

4. Conclusion

The TRIPS Agreement has introduced global standards for the protection and enforcement of IPRs. Some of the provisions may highly impact public health concerns particularly in (L)DCs. Considering the interrelation between health and IP, Member States have further developed the TRIPS flexibilities. These mechanisms, together with the R&D related regulations of the Agreement, provide important opportunities for Member States to develop a policy strategy for pharmaceutical innovation and access to the developed products in a public health sensitive way, including for neglected diseases.

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ing to medicinal products for human use, available at http://ec.europa.eu/enterprise/pharma ceuticals/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf, accessed on 14 September 2009.

The implementation of an EU Directive requires the adaptation of national laws of Member States only according to the minimum standards that are set. This may result in different narrow or broad implementations in the Member States.

In the United States, the "Bolar" exemption has been developed by case law. In *Madey vs Duke University* (307 F.3d, 1351, 2002) the Court confirmed the view in *Roche Products Inc vs Bolar Pharmaceutical Co.* (see footnote 169) and decided that the research exemption was "truly narrow" and "so long as the act is in furtherance of the alleged infringer's legitimate a business and is not solely for amusement, to satisfy idle curiosity, or for a strictly philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defense."

171 WTO Panel Report Canada – Patent protection of Pharmaceutical Products WT/DS114/R (2000). Available at http://www.wto.org/english/tratop_e/dispu_e/7428d.pdf, accessed on 14 September 2009.

IV. World Health Assembly Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property

1. WHO Commission on Intellectual Property Rights, Innovation and Public Health

The inadequacies of the global medicinal innovation system for producing health products for neglected diseases and the recognition of the impact of IP on pharmaceutical R&D and access to existing treatments have raised growing attention to the relationship between IPRs, innovation and public health. In 2004, at the request of the World Health Assembly (WHA)[172], the WHO set up the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) chaired by Ruth Dreifuss, the former President of the Swiss Confederation. The CIPIH was tasked to analyze the interface and linkages between IPRs, innovation and public health, and to examine in depth how to stimulate the creation of new medicines and other products for diseases that mainly affect developing countries.

The Commission published an extensive report in 2006[173]. It recognized the reduction of the very high incidence of infectious diseases disproportionately affecting (L)DCs as overriding priority, alongside with the importance to address the growing number of non-communicable diseases in these regions. The international community was called upon to find, amongst others, ways to tackle more effectively the health needs of poor populations, taking into account both the necessity of improving access to new existing products and the urgency of developing appropriate new health technologies for diagnosis, treatment and prevention.

The report further reviewed the various effects of IPRs, particularly patents, on upstream research, the subsequent development of medical products in both industrialized countries and (L)DCs and the possibility of ensuring access to them in (L)DCs. In industrialized countries, a

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[172] WHA, Intellectual property rights, innovation and public health, WHA Resolution 56.27 of May 2003, para. 2.

[173] CIPIH Report, 2006, *see* footnote 4.

largely self-sustaining innovation cycle may be observed in biomedical R&D, based on positive conditions such as the existence of a large pharmaceutical market underpinned by IP protection, and publicly supported substantial upstream research effort. (L)DCs, however, face weak or non-existing upstream capacities, due to lack of sufficient resources to invest in public sector research, or a private sector with innovative capacity. Thus, (L)DCs, with the exception of few technologically more advanced countries, are mainly dependant on R&D resources and activities in industrialized countries that, however, have failed to address their health needs.

The report further considered the impact of funding and incentive mechanisms, and fostering innovative capacities in (L)DCs. It recognizes the importance of IPRs, particularly patents, as incentive for the development of new pharmaceutical products, however reaches the conclusion that the IPRs do not provide an effective incentive when the targeted patients lack purchasing power.

Based on its findings, the CIPIH developed 60 recommendations for action to improve current incentive and funding regimes to stimulate the creation of new health products and to facilitate access to these and existing medicines. It addressed industrialized countries and (L)DCs, as well as other stakeholders, including the private pharmaceutical and biotechnological sector[174]. Particularly, the Commission recommended that "WHO should develop a global plan of action to secure enhanced and sustainable funding for developing countries and making accessible products to address diseases that disproportionately affect developing countries"[175].

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[174] The recommendations refer to the different stages of the innovation cycle, namely discovery, development and delivery, and include also ways of fostering innovation in (L)DCs. A summary of the recommendations can be found at the pages 175-184 of the CIPIH Report. *Ibid.*

[175] *Ibid.*, recommendation 6.1.

2. WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property

Accordingly, the 59th WHA adopted a resolution requesting the establishment of an intergovernmental working group open to all interested Member States, to draw up a global strategy and plan of action and provide a medium-term framework based on the CIPIH recommendations, which would "aim, inter alia, at securing an enhanced and sustainable basis for needs-driven, essential health R&D relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for R&D, and estimating funding needs in this area"[176]. The resolution also requested the invitation of observers to the process of the intergovernmental working group, including UN organizations, intergovernmental organizations and nongovernmental organizations (NGO) with official relations to the WHO, as well as experts, concerned public and private entities in order to provide advice and expertise where necessary[177].

During the period from December 2006 to April 2008, the Intergovernmental Working Group on public health, innovation and intellectual property (IGWG) met through three sessions with the participation of WHO Member States, intergovernmental organizations, NGOs, and the pharmaceutical industry. Additionally, inter-country and regional consultations in all the WHO regions took place, and two public web-based hearing were held to receive a broad view on the global strategy and plan of actions, also from other interested stakeholders, including, for example, individuals, academic and research institutions, and civil society groups[178].

With consensus on almost all elements, the Global Strategy and agreed parts of the Plan of Action was adopted at the 61st WHA on 24 May

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[176] WHA, Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action, Resolution WHA 59.24, 27 May 2006, para. 3.1.

[177] *Ibid*., para. 3.2., 4.2. and 4.3.

[178] Background documents on the IGWG process, including the reports of the various sessions and hearings, can be found at the WHO webpage http://www.who.int/phi/documents/en/, accessed on 15 September 2009.

2008[179]. The resolution urges Member States to implement the strategy and the plan of action and to provide adequate resources[180]. The WHO was called to support on request the implementation, including through coordinating with intergovernmental organizations such as the WIPO, WTO or UNCTAD; furthermore, to prepare a quick start program; to immediately begin the implementation of action points falling under the WHO responsibility; to establish the expert working group to examine R&D financing and coordination and to consider proposals for innovative funding to stimulate R&D[181].

Up to the present, the outstanding components of the plan of action have been completed. The expert group on R&D financing has been established and has held its first sessions. It will submit its final report to the Sixty-third WHA in May 2010[182].

Furthermore, the WHO has initiated the Quick Start Program. Objectives of the program are, amongst others, to map global R&D activities; to identify research gaps and research priority setting; to support R&D; to develop and strengthen regulatory capacity in (L)DCs; and to develop a monitoring and reporting framework for the implementation of the Global Strategy and Plan of Action[183].

In January 2009, the WHO released the detailed cost estimates for the implementation of the Global Strategy and Plan of Action. It estimated that the costs of strengthening the system for implementing the elements would be about US $ 2,06 billion (covering activities to facilitate coordination, development of norms and standards, information sharing and others), and the costs of undertaking the R&D, innovation and technol-

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[179] WHA, Global strategy and plan of action on public health, innovation and intellectual property, WHA Resolution 61.2, 24 May 2008 [hereinafter Global Strategy and Plan of Action, 24 May 2008].

[180] *Ibid.*, para. 2.1. and 2.2.

[181] *Ibid.*, para. 4.1, 4.2, 4.3, 4.6, and 4.7.

[182] WHO, Expert Working Group on R&D Financing, at http://www.who.int/phi/ewg/en/index.html, accessed on 15 September 2009.

[183] WHO, Executive Board, Global Strategy and Plan of Action – Report by the Secretariat (EB 124/16), 20 November 2008, para. 4-5.

ogy transfer, including education of workers and building infrastructure, at US $ 147 billion[184]. Based on the latter sum it concluded average costs for all Member States of US $ 21 billion per year, additional to those currently being borne.

3. WHA Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property

a) General features

The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA) aims to promote new thinking on innovation and access to medicines, as well as to provide a medium-term framework for securing an enhanced and sustainable basis for needs driven essential health R&D relevant to diseases which disproportionately affect (L)DCs. While focusing on the Type II and III diseases as referred to by the CMH and the CIPIH report, it also considers the specific R&D needs of (L)DCs in relation to Type I diseases[185]. Recognizing the initiatives that have been taken by various stakeholders in recent years to develop new products against diseases prevalent in (L)DCs and to increase access to existing products, the GSPA concludes that these programs are not sufficient to meet the challenges of ensuring access and innovation for needed health products in order to meet the health-related MDGs, and to implement the obligations and commitment according to applicable human rights instruments with health relevant provisions. Thus, it calls to develop proposals for health-needs driven R&D and to explore a range of incentive mechanisms, including models that address the de-linkage of the cost of R&D and the price of the health products and methods for tailoring the optimal mix of incentives to a

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[184] WHO, Public health, innovation and intellectual property: global strategy and plan of action – Proposed time frames and estimated funding needs (EB124/16 Add.2), 21 January 2009, para. 5.

The document further provides costing information for each specific action point.

[185] *See* chapter A. I.1. for the definition of the terms Type I, II and III diseases.

particular condition or product with the objective of addressing diseases predominately affecting (L)DCs[186].

In its principles, the GSPA acknowledges the strategic and central role of the WHO in the relationship between public health, innovation and IP within its mandate, capacities and constitutional objectives. It further makes cautious references to the relationship between health and IPRs, by including the enjoyment of the highest attainable standard of health as one of the fundamental rights of every human being, and referring to IPRs as important incentives for the development of new health products, however, insufficient to meet alone the needs for R&D for diseases with small or uncertain markets. The GSPA further states that IPRs do not and should not prevent Member States from taking measures to protect public health (in view of the Doha Ministerial Declaration on the TRIPS Agreement and Public Health), and requests that international negotiations on issues related to IPRs and health should be coherent in their approaches to the promotion of public health[187].

With respect to R&D, the GSPA calls on industrialized countries to better reflect the health needs of (L)DCs in their R&D efforts and to promote the development of effective, safe, health products of good quality that are affordable and accessible[188].

The GSPA provides eight goals to be achieved in order to promote innovation of and access to medicines:

1) Prioritizing R&D needs of (L)DCs;
2) Promoting R&D for Type II and III diseases and the specific R&D needs of (L)DCs in relation to Type I diseases;
3) Building and improving innovative capacity, particularly in (L)DCs;

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[186] Global Strategy and Plan of Action, 24 May 2008, para. 13, 14.b, 3 and 4.

[187] *Ibid*., para. 15, 16, 25, 20 and 19.

[188] *Ibid*., para. 23 and 24. iii, iv.

4) Transfer of technology;

5) Application and management of IP to contribute to innovation and promotion of public health;

6) Improving delivery and access;

7) Promoting sustainable financing mechanisms;

8) Establishing monitoring and reporting systems.

In addition, the Strategy defines 108 actions to realize its goals and identifies the lead stakeholders to take such actions, as well as further relevant stakeholders. The medium-term time frame for implementation of the specific actions is set by 2015[189]. Governments are lead actors in most of the action points (91/108 actions). The Plan of Action, however, does not provide clarification whether the governments in questions should be of industrialized countries or (L)DCs, nor the specific action of mutual responsibilities. WHO has the second prominent role in the Strategy and is identified as sole lead on ten action points[190], and together with governments and other stakeholders on further 39 points. Considering the discussion on the competences of the WHO to address IP issues during the IGWG process, this outcome provides an important signal as to the international mandate of the Organization with regard to the public health implications of IPRs.

The GSPA allocates little responsibilities to the pharmaceutical industry. Health related industries are lead actors together with governments in three action points, including the promotion of transfer of technology

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[189] WHO, Public health, innovation and intellectual property: global strategy and plan of action – Proposed time frames and estimated funding needs (EB124/16 Add.2), 21 January 2009.

A few exceptions provide a time frame between 2009 and 2010, for example for specific action 2.3.c. encouraging 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.

[190] For example in element 1 of the GSPA – Prioritizing R&D needs, specific actions 1.1.a, b, and c.

and production of health products in (L)DCs through investment and capacity building and identification of best practices; further, to encourage the consideration of policies conducive to access to quality, safe, efficacious and affordable products in (L)DCs[191].

b) Key elements concerning R&D of pharmaceutical products for neglected diseases

(1) Promotion of R&D in neglected diseases

In order to promote R&D in neglected diseases, the GSPA refers in general terms to activities such as the development of strategic research networks, particularly by promoting the cooperation between the private and public sectors on R&D; further, to provide support for national health research programs in (L)DCs, including by long-term funding where appropriate; and the support of the establishment of health-related innovation in (L)DCs[192].

The GSPA further includes as action point the support of basic and applied scientific research on neglected diseases; as well as the support of early-stage drug R&D in (L)DCs[193]. Under this heading interested Member States are also requested to explore the utility of possible instruments and mechanisms for essential health and biomedical R&D, including the proposal of an essential health and biomedical R&D treaty[194].

(2) Access to knowledge and technology of relevance to the public health needs in (L)DCs

Access to relevant knowledge and technology is a prerequisite for R&D, particularly at the discovery stage of the innovation process. To promote and facilitate access accordingly, the GSPA foresees specific actions such

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[191] Global Strategy and Plan of Action, 24 May 2008, specific actions 4.1.a-c. and 6.3.d.

[192] *Ibid.*, specific actions 2.1.a -c.

[193] *Ibid.*, specific actions 2.2.d and e.

[194] *Ibid.*, specific action 2.3.c.

as the **creation of accessible public health libraries,** including publication of public research institutions in order to enhance their availability in (L)DCs by submitting final manuscripts in electronic form to an open database; the **creation of voluntary open data bases and compound libraries** for drug lead identification through screening (with the participation of compound proprietors such as the pharmaceutical industry or research institutions); the **encouragement of appropriate licensing policies** for publicly or donor-funded medical inventions; the consideration to use a "**research exemption**" for public health issues in (L)DCs for countries that have not yet implemented such a regulation into their national patent laws[195]; and last, the consideration of **patent pools** for upstream and downstream technologies to promote innovation of and access to health products[196]. The action point on finding ways to facilitate **access to** research results and **research tools** is also of relevance[197].

(3) Incentive schemes to encourage neglected diseases R&D

To stimulate the development of new health products for neglected diseases the GSPA considered the international regime on IP, and request the exploration and implementation of other incentive schemes where appropriate.

Foremost, specific actions relate to strengthening the capacities in (L)DCs to manage and apply **IP**, and to make full use of the flexibilities to take measures to protect public health as provided in the TRIPS Agreement and subsequent Declarations with health relevance. Accordingly, the GSPA provides specific actions related to the application and management of IP from a public health perspective or in a manner that maximizes health related innovation. This includes, for example, the support of education and training in the application and management of IP under a public health perspective; the development of global databases

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[195] *Ibid.*, specific actions 2.4. a-d.

[196] *Ibid.*, specific action 4.3.a.

[197] *Ibid.*, specific action 2.2.c.

which contain public information on the administrative status of health-related patents; the provision of technical support for (L)DCs with respect to the TRIPS Agreement and subsequent health related Declarations in order to promote access to pharmaceutical products[198].

The GSPA further calls to develop, promote and implement possible incentive schemes for R&D on neglected diseases, including models that de-link the costs of R&D and the price of health products, in order to ensure its affordability in resource-poor countries. As an example, the GSPA refers to **award schemes**, particularly the award of prizes[199]. Further incentive scheme examples, however, are not included.

(4) Support of product development partnerships

One GSPA sub element requests the facilitation and complementation of the maximum use of existing financing, including through public-private partnerships (PPPs) and PDPs, in order to develop and deliver safe, effective and affordable health products. According actions to be taken are the **support of PPPs and PDPs** and other R&D initiatives that are related to neglected diseases, as well as the development of tools to assess periodically the performance of these initiatives and organizations[200].

(5) Clinical trial capacities in (L)DCs

Clinical trials for neglected diseases products are often conducted in (L)DCs. To promote upstream R&D, the GSPA suggests to build capacities for clinical trial conduct in (L)DCs; to promote funding sources for clinical trials for neglected diseases; to establish and strengthen regulatory capacity in (L)DCs; to establish and strengthen mechanisms for ethical review in the R&D process; and to support investment by (L)DCs in human resources, especially in public health education and training[201].

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[198] *Ibid*., para. 35; specific actions 5.1.a, e, c; and 5.2.

[199] *Ibid*., specific actions 3.5.a and 5.3.a.

[200] *Ibid*., specific actions 7.2.c and b.

[201] *Ibid*., specific actions 2.2.f, 3.2.a, 3.3.c, and 3.1.a.

These efforts can particularly be achieved by the encouragement of intensified North-South and South-South partnerships and networks to support capacity building.

4. Conclusion

The GSPA is the first global cooperative framework aimed at addressing a global medical R&D system that has neglected the health needs of poor populations in (L)DCs. It provides a global policy related to public health, innovation and IP that has been described as at least as important as the Doha Declaration. The GSPA emphasizes the need for biomedical innovation for diseases predominately affecting (L)DCs and access to it in these regions. It expresses the importance of developing and implementing innovative mechanisms to provide incentives for health product development. The GSPA further includes the enjoyment of the highest attainable standard of health as principle. Endorsed by all Member States of the WHO (193), it suggests particular potential to advance international cooperation in relation to innovation of and access to health products for diseases in (L)DCs, and may serve as a normative reference in international and national law and policy on innovation for neglected diseases and access to medicines.

Addressing the issues of availability of medicines, their affordability and accessibility in (L)DCs, the GSPA also reflects aspects of the human right to the highest attainable standard of health, and the objectives of the Millennium Declaration and its related MDGs by contributing to better health in (L)DCs as a factor to equalize poverty-related inequalities.

The GSPA is an international agreed consensus on the objectives laid down in the document. It is not legally binding on WHO Member States. They are, nevertheless, called upon to implement the specific actions recommended in the GSPA and to provide adequate resources. The framework contains enough flexibility for a national implementation adapted to the domestic scientific, social and economic context, but also enough guidance to define clear strategies and policies to realize the objectives of the GSPA, namely to secure and enhance sustainable needs

driven R&D for diseases disproportionately affecting (L)DCs, also by implementing incentive schemes for relevant R&D; to improve delivery of and access to all health products in these regions; and to foster innovative capacity building for R&D in (L)DCs. The GSPA further provides a framework for bilateral and multilateral collaboration to address the public health priorities of (L)DCs. Its success depends on the political and financial commitment of the governments in both industrialized countries, where the large part of biomedical R&D proceeds, and (L)DCs, where neglected diseases are predominant.

Furthermore, it requires strong leadership of the WHO to uphold the momentum to ensure implementation and continuing international co-operation in this field, as well as to monitor the progress towards reaching the GSPA objectives. The strategy affirms the role the WHO has to play in the interrelating area of public health, innovation and IP.

Although not the primary addressee in most specific actions of the GSPA, other relevant stakeholders, such as, foremost, the pharmaceutical industry, academia, other research organizations, and charitable foundations are indispensable actors in the realization of the goals and aspirations of the strategy. As holders of particular skills, knowledge and technologies in biomedical R&D, and as members of the (global) society, they also carry high responsibility towards contributing to socially desired outcomes such as a better health for all, specifically including the poor.

The current high awareness of public health issues in (L)DCs at the international level and the various initiatives and frameworks of the international community provide a so far unique situation to progress in global health questions and to find a sustainable way of achieving increased health, social and economic development, particularly for (L)DCs. Actors at all levels should seize this opportunity. Endorsing and implementing the GSPA, is "a contribution to fairness in health "and "pro-active public health at its very best"[202].

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[202] Chan M., WHO General Director, Closing remarks to the 61st WHA, Geneva, 24 May 2008. Available at http://www.who.int/dg/speeches/2008/20080524/en/index.html, accessed on 17 September 2009.

V. Final remark

Neglected diseases have been included in various international frameworks that all provide the basic features of addressing public health concerns in (L)DCs (including pharmaceutical innovation and access to existing health products), insisting on national responsibilities of endemic countries and international responsibilities of countries in the position to assist. The human rights context may provide a rights-based approach to health, including to the area of availability and accessibility of health products to marginalized and poor populations. With the declaration of the MDGs, governments have politically committed to achieve better health for resource-constrained countries and to provide accordingly required resources. While regulating trade aspects and aiming at promoting IP protection for the facilitation of international trade, the TRIPS Agreement addresses the public health needs of (L)DCs. It offers flexibilities for implementation and application of the legally binding provisions of the Agreement in a public health supporting way, including for biomedical innovation and access to the respective products. These mechanisms should be further developed and used where necessary.

The most focused framework in addressing the health needs in (L)DCs is the GSPA, that provides specific actions for various stakeholders to be implemented in order to increase and accelerate R&D efforts for diseases predominately affecting (L)DCs, and access to developed and existing health products. Biomedical and pharmaceutical R&D is mainly carried out in industrialized countries, which implies a particular responsibility of their governments to find ways to implement the strategy elements in a manner that contributes to innovation and access, and as such, to better health of populations in resource-poor countries. Nevertheless, even countries with very limited resources can take some steps to include a research policy independently or in bilateral or multilateral collaboration. Various frameworks to address neglected diseases have been developed and stakeholders are requested to realize them.

C. Incentive mechanisms to stimulate R&D of pharmaceutical products for neglected diseases

The GSPA states that R&D of industrialized countries should better reflect the health needs of (L)DCs. In consequence, Member States are asked to develop and promote new incentive schemes for R&D, including mechanisms that de-link the costs of R&D and the price of health products, such as the award of prizes. Further potential models are voluntary patent pools of upstream and downstream technologies or an essential health and biomedical R&D treaty. As one of the key request, the GSPA addresses all stakeholders to support public-private and product development partnerships. Governments of both the industrialized countries and the (L)DCs are stakeholders in most of the specific actions in the WHA resolution. It appears to be inevitable for Member States to develop a national strategy including various incentive programs based on the economic situation and competitive advantages a country provides, however, also in view of international programs that exist or will be established to support neglected diseases R&D. This chapter examines the incentive schemes included in the GSPA and other mechanisms that are internationally discussed to foster product development for diseases disproportionately affecting (L)DCs.

I. Incentive role of patents and the TRIPS Agreement

Differentiating between global diseases that are prevalent in industrialized and developing countries, such as HIV/AIDS, and diseases epidemics in (L)DCs only, the patent system in industrialized markets already provides substantial incentives to finance R&D for the first group of conditions while further market options in (L)DCs are rather irrelevant[203]. For diseases prevalent in (L)DCs only, the IPR will not suffice to

[203] Investments in R&D on HIV/AIDS, for example, accounted for U.S. $ 3.6 billion in 2004, despite the fact that the majority of the infected live in (L)DCs, and regardless of patent protection in poor countries. *See* Kates J., Kaiser Family Foundation, Financing the response to HIV/AIDS in low- and middle-income countries: Funding for HIV/AIDS from the G7 and the European Commission. Presented at: Post G8 Briefing: Future financing to address the

encourage private R&D investment, because of the absence of a high-income market to recover R&D costs and low purchasing power of consumers. The exclusive power conferred by a patent to set high prices is of no value if patients or governments cannot pay[204]. To address their specific demands in pharmaceuticals that differ from those in the industrialized world, (L)DCs, in the majority of cases, lack innovative capacities and finances to provide market-based incentives; moreover, pharmaceutical research and manufacturing facilities are limited and the private pharmaceutical sector is not robust enough to participate directly in R&D[205].

Negotiating the TRIPS Agreement, the introduction of strong patent protection for pharmaceutical research (product and process protection) in (L)DCs was seen as essential to stimulate domestic and international firms in order to establish R&D facilities that would promote technological development, and furthermore, to encourage private companies' investment in the development of drugs of specific need in those countries[206]. The basic objective of the TRIPS Agreement, according to its article 7, is that "the protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare". This role of intellectual property, and in particular of patents, in fostering innovation and economic growth, and its impact on the development process of (L)DCs, however, remains an area of conflicting views. It has been argued that the significance of patent protection for promoting innovation and economic growth within a country

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global HIV/AIDS epidemic, Washington, DC, July 2005. Available at http://www.kff.org/hivaids/upload/Financing-the-Repsonse-to-HIV-AIDS-in-Low-and-Middle-Income-Countries-Funding-for-HIV-AIDS-from-the-G7-and-the-European-Commission-Chartpack.pdf, accessed on 15 October 2008.

[204] Danzon P.M., Towse A., p. 184.

[205] CIPIH Report, p. 164.

[206] Lanjouw J.O., MacLeod M., Pharmaceutical R&D for low-income countries – Global trends and participation by Indian firms, CIPIH study paper 2005, pp. 4, 6 [hereinafter Lanjouw et al., 2005].

would depend on the level of the country's development[207]. Evidence from literature suggests that a patent system is of little or no value to impoverished and unindustrialized countries without local scientific and technological infrastructure and lack of financial resources devoted to innovation[208]. In countries with some technological capabilities, intellectual property policy is dominated by the interest to foster low-cost imitation and weak protection of intellectual property to allow indigenous companies to use imported technologies efficiently by imitation and reverse engineering. Some even argue that tightening intellectual property protection through the globalization of minimum protection standards by TRIPS may slow the diffusion of technology to developing and least developed countries that has traditionally been generated by imitation and reverse engineering[209]. Rapid growth of countries appears to be more associated with weak intellectual property rights[210].

Strengthening intellectual property protection and enforcement becomes more favorable for domestic companies and governments as economies advance to a higher income range with local inventive and absorptive technological capabilities. A positive effect on medicinal R&D is assumed to be observed in countries such as India, Brazil or China, with already existing innovative capacity in the pharmaceutical sector. Emerging market opportunities and access to low-cost R&D resources as well as high-skilled developing country researchers increasingly attract in-

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[207] World Bank, Intellectual property: balancing incentives with competitive access, Global Economic Aspects, 2001, pp. 129, 130; Report of the Commission on Intellectual Property Rights, Integrating intellectual property rights and development policy, London 2002, p. 25 [hereinafter CIPR Report, 2002]. Lall S., Indicators of the relative importance of IPRs in developing countries, UNCTAD-ICTSD Project on IPRs and Sustainable Development, Issue Paper No. 3, June 2003, p. 10 [hereinafter Lall S., 2003].

[208] *Ibid*.; Maskus K.E., Encouraging international technology transfer, UNCTAD-ICTSD Project on IPRs and Sustainable Development, Issue Paper No. 7, May 2004, p. 26.

[209] Sachs J., The global innovation divide, in Jaffe A., Lerner J., Stern S., eds., Innovation policy and the Economy: Volume 3, MIT Press, Cambridge MA, 2003, pp. 131-141; CIPR Report 2002, p. 22.

[210] CIPR Report, 2002, p. 22.

volvement of multinational companies[211]. Studies aiming to determine whether strengthened IP rights in countries such as India have also influenced domestic innovation behavior suggest a rapid growth in overall investment in pharmaceutical R&D over the past years (since 2000)[212]. Nevertheless, the focus of the local pharmaceutical industry is directed towards global diseases with distinct industrialized market potential. Despite the fact that a very large population is affected by neglected diseases in India, investments towards the specific health needs of (L)DCs have decreased in the country[213]. This development conflicts with the assumption that strong intellectual property rights in (L)DC economies without domestic technological base would stimulate global innovation by adding effective demand for new products for developing countries' needs. The specific products needed by poor countries represent only a small fraction of global demand due to small markets and little profitability expectations. It is rather unlikely that global R&D would rise with stronger intellectual property rights in these countries or that it would address their specific needs[214]. Referring to global pharmaceutical innovation for neglected diseases, the patent system has proved to be inappropriate to stimulate pharmaceutical R&D[215]. In the absence of a commercial market, patent protection is not a sufficient encouragement for innovation performed by private sector pharmaceutical companies in industrialized, but also emerging countries such as India which have a local pharmaceutical industry. The development of health tools for diseases affecting developing countries occurs rather in cases of philanthropic or public funding involvement[216].

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[211] London School of Economics and Political Science, The new landscape of neglected disease drug development, September 2005, p. 9 [hereinafter LSE Report, 2005].

[212] Lanjouw et al., 2005, pp. 4, 6; also CIPIH Report, p. 101.

[213] Lanjouw et al., 2005, p. 6.

[214] Lall S., 2003, p. 11.

[215] CIPR Report, 2002, p. 22; Saggi, K., Trade, Foreign Direct Investment and International Technology Transfer: A Survey, World Bank Policy Research Working Paper (WPS2349), Washington DC 2000, pp. 18 ff.

[216] CIPIH Report, 2006, p. 101.

More than ten years after the TRIPS Agreement took effect, the innovation and capacity building gain for most (L)DCs is of moderate extent in the pharmaceutical field. Future prospects are not very bright either, taking into account that most countries have virtually no capabilities to contribute to the development and costs of major drugs for their specific demands before long. Moreover, as summarized in the CIPIH report, there is no evidence that the implementation of the TRIPS Agreement in (L)DCs will significantly increase R&D in pharmaceutical for diseases predominately or exclusively incident in (L)DCs, because of insufficient market incentives as decisive factor[217]. In the absence of a commercial market, patent protection is not a sufficient encouragement for innovation.

II. Push and pull incentives for neglected diseases R&D

The classic model of governments to react on market failures, such as in the case of lack of pharmaceutical products for certain diseases, is to provide market incentives for the private sector to increase investments in the area of need. To encourage R&D for prevalent diseases, a combination of "push" and "pull" measures is employed. Push programs are designed to directly support research inputs, thus decrease the cost of development of products[218]. They include direct public research funding; creation of public research programs; grant programs; special tax breaks (for neglected diseases) for R&D expenditures; or targeted R&D funds for specific R&D performance. Public or philanthropic push mechanisms are basically directed towards basic research. For the application of research results, however, pull incentives are necessary to take the development of new health technologies from basic science through the next stages up to the clinical development and product launching. Pull mechanisms reward the innovator for generating socially desired prod-

[217] CIPIH Report, 2006, p. 102.

[218] Ridley D.B., Grabowski H.G., Moe J.L., Developing drugs for developing countries, Health Affairs, Vol. 25 No. 2, March/April 2006, p. 316.

ucts, thus increase financial returns[219], motivating R&D involved companies to select projects with the best prediction for success as exploitable products. Certain market conditions provide pull incentives for R&D, such as intellectual property protection, national health insurance schemes and payment policies, price setting opportunities, market size, or purchase agreements for developed products. They can alter the prospects for future revenue and play a key role for investment determination[220].

1. Orphan drug regulation incentives

An example of successful synergy between push and pull incentives to foster pharmaceutical R&D is the legislation on orphan drugs, that has been enacted in the United States, the European Union, Australia and other countries. Orphan drugs are health tools for the diagnosis, prevention and treatment of rare disorders. Characterized by a low prevalence[221], genetic transmission and heterogeneity, the rare diseases face a lack of public awareness and public health priority. In addition, the small number of patients affected by these diseases provides too little market opportunities for commercial pharmaceutical R&D and results in a lack of medicinal products. Orphan drug regulations (ODR) have been put in place in consideration of equity in public health, acknowledging that patients with rare diseases have the same right to adequate treatment as others. Incentives provided in the legislations include push factors such as: regulatory authority "fast track" programs; regulatory authority counseling during the clinical study phases; a common application procedure for the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA) for an orphan designation of the same medicinal product for the same use in both jurisdictions; waiver of

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[219] *Ibid.*, p. 316.

[220] United States Congressional Budget Office, Research and development in the pharmaceutical industry, October 2006, p. 7.

[221] According to the legal numeric definition, diseases are rare if they affect 7.5 persons in 10.000 people in the United States and respectively 5 persons in 10.000 in Europe.

registration fees; R&D tax credits and clinical research grant programs (United States), all included to reduce the high fixed costs of drug R&D. The long market exclusivity for several years (for example seven years in the United States, or ten years in the European Union) provided for the orphan drug designation is considered as a compelling pull mechanism and a strong incentive for pharmaceutical R&D investment. The regulatory authority will not issue marketing authorization for any similar medicinal product in the same therapeutic field for the regulated period. Market exclusivity is granted independently of any intellectual property rights on the product, and can be applied to existing products that are no longer under patent protection or that or not patentable[222].

The orphan drug regulations have been described as a successful intervention to foster R&D investments for rare disorders. In the United States, for example, more than 320 products for various rare diseases have been developed by the private sector within 25 years, versus 34 products, mainly publicly financed, before the introduction of the Orphan Drug Act[223]. Some of the products have become a commercial success[224]. The profitability of the drugs is enabled by the exclusivity status granted by the orphan designation and the subsequent high product prices. The market for the medicinal products in industrialized countries is guaranteed by the third party payments of insurance companies or State funded health insurance systems. Moreover, studies demonstrate

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[222] An example for the lack of patentability are products that do not receive patent protection because they were synthesized and their structure was published before the discovery of their medical use, *see* Villa S., Compagni A., Reich M.R., Orphan drug legislation: lessons for neglected diseases, International Journal of Health Planning and Management, 2009, vol. 24, p. 33. At http://www.wcfia.harvard.edu/sites/default/files/Reich_Orphan.pdf, accessed on 5 August 2009 [hereinafter Villa et al. 2009].

[223] U.S. Food and Drug Administration, Cumulative List of All Orphan Designated Products Approved for Marketing, at http://www.fda.gov/orphan/designat/allap.rtf, accessed on December 2008.

In Europe the number of orphan-designated products has raised to 50 as of November 2008. *See* European Medicines Agency, List of orphan-designated authorized medicines, 6 November 2008. Available at http://www.emea.europa.eu/pdfs/human/comp/56357508en.pdf, accessed on 5 July 2009.

[224] For example Cerezyme for Gaucher's Diseases, or the cancer drug Gleevec, Villa et al. 2009, pp. 33, 34.

that the majority of the rare diseases drugs were developed by small or medium-sized biotechnology companies[225].

Some neglected diseases may be included under the ODRs based on few cases that occur in industrialized countries through returns of infected citizens from travels to endemic areas, opening up the application of the administrative and financial incentives provided by the legislations. Nevertheless, in the United States, for example, the Orphan Drug Act has been applied only to a few cases so far since its existence from 1983[226]. For neglected diseases, the economic incentives of the legislations, and particularly the market exclusivity, as principal motivating instrument, have not resulted in the same achievements as for the rare diseases. The regulations intend to create a market for products for small populations living in affluent countries with the ability to pay for developed products or comprehensive third party payment, thus providing some profitability expectations trough a time limited market exclusivity. In contrast, neglected diseases affect large population groups in resource-poor countries with low or no purchasing power or deficient social security systems. Endemic countries lack the commercial security and price setting opportunity that industrialized countries can enjoy. Thus, the grant of market exclusivity for a neglected disease product does not address the absence of markets in developing countries and does not provide the same strong incentive effect as established for rare diseases. Moreover, the potential value of an orphan drug designation in terms of annual revenue per patient is much higher for medicinal prod-

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[225] Haffner M.E., Adopting orphan drugs - two dozen years of treating rare diseases, New England Journal of Medicine, Vol. 345, 2006, pp. 445-447; European Committee for Orphan Products (COMP), Report on the first 3-year mandate of the European Committee for Orphan Products, April 2003, pp. 29-32.

[226] For the orphan drug designations and product registrations between 1983 and 1997, *see* Trouiller P., Battistella C., Pinel J., Pecoul B., Is orphan drug status beneficial to tropical disease control? Comparison of the American and future European orphan drug acts, Tropical Medicine and International Health, Vol. 4, June 1999.

ucts against chronic diseases that require a life-long treatment than for acute communicable diseases with a shorter therapy period[227].

Despite these drawbacks of applying the orphan drug regulations (ODR) to neglected diseases there have been recent cases of orphan drug designations for this therapeutic field showing a new emergence in using the laws, but also how creative business models or arrangements successfully contribute to the development of products for neglected diseases.

In one case the Oxford University received the orphan drug status by the EMEA for its developed tuberculosis vaccine in 2005. For the first time the orphan drug designation has been awarded on the grounds of insufficient return on investment which may demonstrate a potential avenue for other applications to health products developed specifically for poverty related disease in (L)DCs[228]. Based on the orphan drug status the university became eligible for the European ODR incentives.

The vaccine has entered the clinical trial phase II in 2009, supported by a partnership between various stakeholders, including a Consortium consisting of the Oxford University and a biotechnology company, the Aeras Global TB Vaccine Foundation, a not-for-profit Product Development Partnership, and donors, such as the Wellcome Trust and the BMGF, and others. The clinical trial will be carried out in South Africa in collaboration with local partners[229].

In the second case, 2005, the Institute for OneWorldHealth (iOWH), a non-profit pharmaceutical company was awarded an orphan drug designation by the FDA and the EMEA for Paromomycin for the treatment for viscal Leishmaniasis[230]. The iOWH developed the compound that

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[227] Diseases Control Priorities Project, Chapter 6, Product Development Priorities: Financing and institutional arrangements for new product development. Available at http://www.dcp2.org/pubs/DCP/6/Section/737, accessed on 5 July 2009.

[228] Lang T., Hill A.V.S., Sha R., Towse A., New TB vaccine granted orphan drug status, BMJ 331, 2005, p. 1476.

[229] University of Oxford, TB vaccine enters new clinical trials, 23 April 2009. At http://www.ox.ac.uk/media/news_stories/2009/090423.html, accessed on 13 August 2009.

[230] Hale V., Treating neglected diseases – The role of orphan drugs. At http://www.pharmafocusasia.com/strategy/treating_neglected_diseases.htm, accessed on 13 August 2009.

was off-patent in partnership with the WHO Special Programme for Research and Training in Tropical Diseases (TDR) and funding from the BMGF. The product was approved in 2006 in India, one of the countries with the highest visceral leishmaniasis prevalence, and is since 2007 on the WHO's Model List of Essential Medicines[231].

Both cases show successful uses of the ODR in combination with innovative business arrangements for product development for diseases with no efficient market in industrialized countries. The orphan drug status may not notably stimulate R&D in neglected diseases but the ODRs could provide an instrument to support and reward respective initiatives[232].

2. Push and pull incentives for neglected diseases R&D

a) Push incentives

The need for additional or alternative incentives to redirect medicinal R&D also to the field of neglected diseases has been discussed widely at the international level. The common push mechanisms used in the orphan drug regulations (ODRs) may be employed for neglected diseases. They are designed to accelerate the R&D process, as well as to decrease related expenditures. The general advantage of push measures is that the required funding for the implemented instruments is lower than for pull instruments. They can be received independently from the success in product development, which reduces the uncertainty for the developer; furthermore, the incentives are immediately available, credible and, particularly, push programs do not require a budget line (increasing acceptability of the incentive)[233]. However, for government authorities it creates the difficulty to decide before the development of the product on the most promising program and R&D direction. In many cases authorities

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[231] iOWH Webpage, http://www.oneworldhealth.org/leishmaniasis, accessed on 13 August 2009.

[232] Villa et al. 2009, p. 40.

[233] Consultation document by Marti J., Jeanrenaud C., Institute for Research in Economics, University of Neuchâtel, 2009 [hereinafter Consultation document, 2009].

may lack adequate information to make the choice. In addition, push mechanisms provide financial support for research inputs and not research results, leaving the risk of failure with the government. Last, push programs provide less opportunities of controlling or supervising the R&D activities[234]. Besides these general disadvantages, they nevertheless offer forms of governmental support for R&D in areas with no commercial incentives, as already established, for example in the case of orphan diseases.

The push incentives include, as provided in the ODRs and discussed above, parts of the **regulatory authority process** (related to neglected diseases R&D activities), such as a fast track procedure for products developed for neglected diseases, protocol assistance for clinical trials, and waivers of registration fees.

Other government interventions are financial and fiscal policy mechanisms. They may be offered in forms of **research grants** and **tax credits**.

Research grants may be provided to companies active in the neglected diseases product development, for example for clinical trial activities. Model examples are the French Hospital Programme for Clinical Research that included rare diseases as priority[235], and the U.S. ODA Research Grant Program[236], both intending to encourage the clinical development of products for use in rare diseases.

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[234] *Ibid*.

[235] In 2002, 22 clinical research programs were funded over three years with grants ranging from 75.000 Euro to 640.000 Euro pro project. The budget provided for the period from 2005-2008 made 22.5 million Euro available. *See* European Commission, Inventory of Community and national incentive measures to aid the research, marketing, development and availability of orphan medicinal products, Revision 2005. Available at http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory_2006_08.pdf, accessed on 6 July 2009 [hereinafter European Commission, Revision 2005], p. 13.

[236] The annual FDA budget for funding the grants is approximately $13 million. Clinical trials are awarded grants from $200, 00 (Phase 1) to $350,000 (Phase 2 and 3) per year in total costs for up to 3 years. Ongoing studies are financed first. Applicants may be from public, private, not-for-profit, and for-profit organizations. *See* webpage of the FDA, Office of Orphan Products Development Grant Program, at http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/ucm134580.htm, accessed on 6 July 2009.

Fiscal incentives are increasingly offered by OECD governments to increase spending on R&D, largely because R&D and innovation are considered key to productivity and growth performance[237]. **Tax credits** can be provided in various schemes. Many countries use targeted tax incentives for small and/or medium-sized companies (SMC)[238], or tax incentives for companies that collaborate with qualified public research institutions or fund the latter[239]. Often, pharmaceutical companies can also apply special tax credits available only for firms that undertake certain kinds of R&D, such as the United Kingdom tax incentive program for the development of vaccines and medicines for TB, malaria, and HIV/AIDS[240], or, as already mentioned, orphan drug tax credits provided in various national legislations[241]. In the United States, a legislative proposal, the Vaccines for the New Millennium Act 2001, provides a 30 percent tax credit for R&D expenses for vaccines for HIV, tuberculosis, malaria or any infectious disease, which, according to the WHO, causes more than one million human deaths annually[242].

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[237] OECD, Tax incentives for Research and Development, Trends and Issues, 2003, pp. 1-37.

[238] For example Belgium, United Kingdom, Netherlands, Norway or the United States.

[239] For example the Denmark, Norway, the United States.

[240] United Kingdom Vaccine research relief, Schedule 13 to the UK Finance Act 2002. Available at http://www.opsi.gov.uk/acts/acts2002/ukpga_20020023_en_26#sch13, accessed on 19 September 2007. The tax relief gives an additional deduction on top of the normal R&D relief in the form of a 50 percent enhancement of qualifying expenditure. In the case of SME it can result in a payable tax credit.

[241] For example, the U.S. orphan drug tax credit provides a 50 percent tax credit for eligible clinical R&D on drugs with an orphan drug designation, 26 U.S.C. Section 45 C (Internal Revenue Code).

In Europe, tax incentives for rare diseases are defined at State level. Tax credits for research or industry are granted in France, The Netherlands and United Kingdom. French tax provisions for example exempt sponsors of orphan drugs from the tax on direct sales and distribution of medicines, the tax on the promotion of pharmaceuticals, based on the promotion costs of laboratories. *See* European Commission, Revision 2005, pp. 7 ff.

[242] United States, H.R. 1504 Vaccines for the New Millennium Act of 2001, introduced April 4, 2001. At http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_cong_bills &docid=f:h1504ih.txt.pdf, accessed on 11 August 2009.

The Act also establishes the Lifesaving Vaccine Purchase Fund to buy vaccines when they become available.

The incentive effect of tax credits to stimulate R&D in areas with uncertain markets, however, is disputed[243]. As a push program the tax incentive rewards research inputs and not research results. This may lead to some drawbacks that are inherent in push programs. Moreover, tax credit programs do not address the question of access to the developed product. The IPRs remain with the developer, and as such the opportunity to set the price that might be too high for populations in developing countries. Additionally, tax credits may not stimulate pharmaceutical companies to develop products appropriate for the environment in resource-poor countries. For example, in the case of malaria, it could provide a stimulus to create a vaccine for the traveler market and military demand. This research might concentrate on a prevention tool for temporary protection only, while people in the endemic countries are permanently exposed to the infection risk and would need another product focus. The consideration to target the tax credit on certain research might display another setback. Research might focus only on the incentive objective (the defined diseases, for example) while another scientific use that might be also a result out of the targeted research would not be discovered. Last, tax credits do not provide benefits for biotechnology companies that in many cases do not have current taxable profits or tax liabilities.

Further models to set off the development costs and facilitate R&D beyond the ODR push incentives are **patent pools** for essential technologies related to neglected diseases, or **social licensing strategies** of public sector institutions or pharmaceutical companies to benefit innovation related to diseases predominately affecting the developing countries.

A **patent pool** is the concentration of licenses of patents of two or more companies. This agreement can have different forms. One common option is the cross-licensing of relevant technology to each of the other patent owners. In the second frequently used form, patent holders assign their individual IPRs covering technology of use in the industry to a central entity, which is responsible for the exploitation of the rights. In turn,

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[243] CIPIH Report, 2006, p. 103.

all pool members are allowed to use any other member's technology. In addition, the group of patents may also be licensed as a package to a third party. The third party pays royalties to the administrating organization that, in turn allocates the royalties to the patent holders.

Patent pools have risen often in the past in other industry sectors than the pharmaceutical industry[244]. Some were reinforced by the government[245], however were more often privately formed by the patent holders[246]. Evidence suggests social and economic benefits of patent pools[247]. Various advantages are associated with pool arrangements, as for example, the elimination of patent thickness, the possibility of lower prices, lower transaction costs of negotiating and administering licensing programs, and managing or eliminating litigation risks[248]. Moreover, patent pools may foster the distribution of technical knowledge and information related to patented technology among pool members, which, in turn, contributes to better access to information in order to use limited resource, that are assumed for example for the biotechnology sector, more efficiently. In consequence, these factors can encourage collaborations and co-operations in a certain field and facilitate and spur the development of new technologies[249]. However, patent pools rely, in gen-

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[244] For example, sewing machines (1856), aircraft (1917), or radio technology (1924), *see* Bekkers R., Iversen E., Blind K., Patent pools and non-assertion agreements: coordination mechanisms for multi-party IPR holders in standardization. At http://www2.unil.ch/easst2006/Papers/B/Bekkers%20Iversen%20Blind.pdf, accessed on 7 August 2009 [hereinafter Bekkers et al., 2006]; Clark J., Piccolo J., Stanton B., Tyson K., Critharis M., Kumin S., Patent pools: A solution to the problem of access in biotechnology patents?, United Sates Patent and trademark Office, 2000, p. 4 [hereinafter Clark et al., 2000].

[245] Merges R.P., Institutions for Intellectual Property Transactions: The Case of Patent Pools, 1999 Revision, p. 27 [hereinafter Merges, 1999].

[246] More recent examples are the privately formed patent pools in consumer electronics include the MPEG_2 technology, among others, between Trustees of Columbia University, Fujitsu Limited, General Instrument Corp., Mitsubishi electric Corp., Philips Electronics N.V., and Sony Corp. (1997); or the DVD-ROM and DVD-Video formats between Toshiba Corporation, Hitachi Ltd., Time Warner Inc., and others (1999). *See* Clark et al., 2000, p. 7.

[247] Grassler F., Capria M.A., Patent pooling; Uncorking a technology transfer bottleneck and creating value in the biomedical research field, Journal of Commercial Biotechnology, Vol. 9, 2003, pp. 111-118.

[248] *Ibid*.

[249] Clark et al., 2000, p. 11.

eral, on the voluntary commitment of the patent holders, thus provide no solution in cases where the proprietor refuse to grant (reasonable) licenses. Additionally, finding the right balance between the cost of creating a pool and the return on investment is a major design challenge[250]. Finally, as coordinated conduct of market actors, patent pools can develop anti-competitive effects and by this infringing competition laws. They would have to be carefully constructed to circumvent this legal issue.

The positive effects of patent pools and evidence from past experiences, nevertheless, suggest this mechanism as an interesting option for government policy to encourage companies to consolidate their IPRs. In some cases this can be an alternative to obliging government interventions such as compulsory licensing[251].

In the pharmaceutical sector no patent pools has yet been established. However, the above mentioned advantages are assumed also at least for the biotechnology industry[252]. For neglected diseases R&D with little market incentives and scare financial resources patent pooling would have the effect of enabling access to technologies that otherwise would be complicated to identify, tracking and license, and, furthermore, of reducing transaction costs [253]. The constitution of a patent pool for diseases affecting least developing countries has been recently proposed by a large pharmaceutical company[254]. The firm agreed at the same time to contribute its own patents for technologies (small molecule compounds or process patents) that might be of relevance for research into malaria, cholera, and other diseases. The emphasis was laid on the voluntary form of the pool to encourage the participation of other stakeholders,

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[250] Bekkers et al., 2006, p. 49.

[251] Merges, 1999, p. 27.

[252] Clark et al., 2000, p.11.

[253] CIPIH Report, 2006, pp. 65, 68.

[254] Witty A., CEO GlaxoSmithKline, Big pharma as a catalyst for change, February 13, 2009 Speech to Harvard Medical School. Available at http://www.hcp.med.harvard.edu/files/Big%20pharma%20as%20a%20catalyst%20for%20change_EMBARGOED%20until%2013_02_09%2014%2000%20EST.pdf, accessed on 7 July 2009.

whilst focusing on least developed countries. Another recent initiative is the Medicines Patent Pool launched by UNITAID[255] in 2008. This pooling agreement[256] will initially concentrate on antiretroviral medicines (ARV), however with the perspective to expand it to other diseases. It aims to promote, among others, an increased access to newer ARVs, the development of adapted formulation for example for children and the reduction in prices for the ARVs by stimulating generic production. It will be designed as a voluntary mechanism with developing countries as geographical target[257]. So far, the Medicines Patent Pool has received the support of, among others, the Government of the United Kingdom[258] and civil society groups[259]. The reaction of the industry remains divided[260]. It might be worth noting that the same company that suggested the

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[255] UNITAID is an international drug purchasing facility focusing on HIV/AIDS, malaria, and Tuberculosis. It was established to support existing efforts to achieve the UN MDGs (Goal 4 – Child Health; Goal 5 – Maternal Health; Goal 6 – Combating HIV and other diseases). *See* http://www.unitaid.eu/.

[256] UNITAID, The Medicines Patent Pool initiative. Available at http://www.unitaid.eu/images/projects/PatentPool/patent%20pool%20english%2015%20may%20revised.pdf, accessed on 7 October 2009.

[257] The pool is expected to provide a win-win situation for the originator pharmaceutical company that would receive a proportion of the royalties; for the generic firms that have facilitated access to the technology; and the affected population in developing countries that obtains affordable and qualitative treatments faster. *Ibid*.

[258] Boseley S., International development minister urges firms to pool HIV patents, The Guardian, 12 July 2009. At http://www.guardian.co.uk/world/2009/jul/12/hiv-medicine-patents-drugs-companies, accessed on 9 August 2009.

[259] Médecins Sans Frontières (MSF), Campaign for Access to Essential Medicines, MSF welcomes UNITAID patent pool endorsement, Press release. Available at http://www.msfaccess.org/media-room/press-releases/msf-welcomes-unitaid-patent-pool-endorsement/, accessed on 9 August 2009. Knowledge Ecology International, Annex 1 – Cost-benefit analysis for UNITAID patent pool, 20 June 2008, Available at http://www.keionline.org/misc-docs/1/cost_benefit_UNITAID_patent_pool.pdf, accessed on 9 August 2009.

[260] Positive responses came from the companies Gilead and Merck, as well as some Indian firms. One major opponent is the company GlaxoSmithKline, while Abbott expressed certain concerns without clearly taking position. *See* BBC News, Drug firms "must pool patents", 15 July 2009. Available at http://news.bbc.co.uk/2/hi/health/8150457.stm, accessed on 7 August 2009. Furthermore, for the Indian pharmaceutical industry, Alexander J., Indian companies welcome UNITAID patent pool for HIV medicines, Pharmabiz, 10 July 2009. Available at http://www.pharmabiz.com/article/detnews.asp?articleid=50624&sectionid=, accessed on 7 August 2009.

patent pool for neglected diseases opposes the UNITAID pooling agreement. After all, HIV/AIDS provides a strong global market for related drugs, which is not the case for neglected diseases with developing country markets only. An assumption might be that for unprofitable areas such as tropical infectious diseases the pharmaceutical companies are more likely to consolidate their IPRs with focus on developing countries as geographical target. All in all, the emergence of patent pool initiatives for pharmaceutical technologies related to developing countries suggest an increased interest, as well as a certain degree of willingness within the industry sector to consolidate their IPRs. The promotion of pool arrangements for health technology relevant for diseases affecting resource-poor countries might be an avenue for policy makers well worth to be considered.

Sensitive and creative licensing strategies of all actors involved in biomedical R&D can also facilitate access to relevant technologies for diseases affecting developing countries and lower development costs. This includes the use of options such as patent donations, non-exclusive licenses or dual market opportunities, which intend to provide a beneficial license to organizations involved in neglected diseases R&D for the developing country market while reserving the affluent market opportunity for the licensor.

Of particular interest is the patenting and licensing policy of public research institutions. Various studies demonstrated that public sector research, including universities, is essential for the development of new health tools. They often hold IPRs to key technologies of many end products. These components are typically licensed to private sector companies for further development. In the United States, for example, publicly funded research has laid the foundation for the discovery of the majority of the most influential drugs in the United States between 1965 and 1992[261]. Universities were proprietors of patent rights in important

[261] Cockburn I., Henderson R.M., Publicly funded science and the productivity of the pharmaceutical industry, in A. Jaffe, J. Lerner, S. Stern (eds.), Innovation Policy and the Economy, Vol. 1, MIT Press for the National Bureau of Economic Research, Cambridge MA, 2001, pp. 20-21.

therapeutic areas such as cancer, anemia, or HIV/AIDS. In view of their important position as upstream technology innovators in the biomedical R&D, public research institutions, and as such universities, can and do play a vital role in the access to technologies with relevance for developing countries. In some cases academic institutions (in the United States) have licensed inventions under favorable conditions to not-for-profit organizations. An example is the license agreement between Yale University, the University of Washington and the non-profit pharmaceutical company Institute for OneWorldHealth. The universities licensed high-potency compounds to treat Chagas diseases to the non-profit organization. The licensing agreement also included a dual market opportunity in which Yale and the University of Washington could develop the same compound for fungal infections in industrialized countries[262]. Some further licensing strategies proposals that are discussed include the negotiation of license clauses such as the requirement of resource-poor country development of products; control over prices; or mandatory sublicensing regulations obliging the manufacturer to license the innovation to another if it cannot deliver a product at an affordable price to resource-poor regions[263]. Other academic institutions have developed specific policies related to the patenting and licensing of technologies of interest to developing countries, such as the Socially Responsibility Licensing Program of U.C. Berkeley, which has the goal to promote the widespread availability of technology and health care in the developing world and to encourage additional investments by others to achieve this goal[264].

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[262] *See* "Institute for OneWorldHealth licenses potent therapy from Yale and University of Washington to treat Chagas, one of the largest parasitic diseases in the world". Available at http://www.oneworldhealth.org/press_releases/release/pr_1226364810, accessed on 15 December 2008.

For further example *see* CIPIH Report, 2006, p. 72.

[263] Nelson L., The role of university technology transfer operations in assuring access to medicines and vaccines in developing countries, p. 307; Stevens A.J., Effort A.E., Using academic license agreements to promote global social responsibility, les Nouvelles, Journal of the Licensing Executives Society International, June 2008, pp. 92-96 [hereinafter Stevenson et al., 2008].

[264] The Program provides guidelines for licensing on innovation applicable to nontraditional markets, such as in developing countries. Agreement models established under the guide-

The examples of social licensing at universities, however, remain few. The integration of such clauses into the license practice of the academic institutions is still at the beginning. To extend the use of a social or humanitarian licensing approach at universities, an advocacy group named Universities Allied for Access to Essential Medicines is calling on the academic institutions to promote equal access to research; to promote R&D for neglected diseases; and to measure research success according to impact on human welfare[265]. Some literature suggests making social responsible licensing a formal institutional policy at universities[266]. A motivating factor may be that some pharmaceutical and biotechnology companies have also adapted humanitarian licensing activities. They include voluntary licensing programs for ARVs to local manufacturers to produce and sell generic versions of some products and market them[267]; and further, the transfer of manufacturing technology and expertise for a tuberculosis treatment to four pharmaceutical firms in the countries with the highest diseases burden[268].

Nevertheless, the acceptance of social license clauses by the pharmaceutical and biotechnology companies could be difficult to achieve. Firms appear to be rather reluctant to sign agreements that may limit their full use of the licensed IP rights even for not-for-profit research[269]. In addition, governments increasingly insist that research organizations seek commercial, co-financing relationships with industry as a mechanism for

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lines include intellectual property licenses, sponsored research agreements and collaborative research agreements. They are structured to provide an economic incentive to licensees to develop and distribute goods and services to low-income and middle-income countries. *See* Office of Intellectual Property and Industry Research Alliances, Socially Responsible Licensing Program, U.C. Berkeley. Available at http://ipira.berkeley.edu/docs/sociallyresponsible11-07.pdf, accessed on 15 December 2008.

[265] Universities Allied for Essential Medicines (UAEM), Philadelphia Consensus Statement, Towards increasing access to medicines, at http://essentialmedicine.org/cs/statement, accessed on 7 August 2009.

[266] Stevens et al., 2008, p. 89.

[267] GlaxoSmithKline and Gilead, *see* Stevens et al., 2008, p97.

[268] Eli Lilly MDR-TB Partnership. The transfer of technology included companies in South Africa, China, India and Russia. *See* Stevens et al., 2008, p. 97.

[269] Stevens et al., 2008, p. 98.

ensuring the practical relevance of the research the institutions carry out. State policies that aim to improve the effective exploitation of publicly funded research results often fail to address a committed humanitarian license approach, leaving it to the responsibility of the individual institute and its technology transfer office to find the difficult balance between the mandate to commercialize the innovation and a global social responsibility[270].

b) Pull incentives

Push incentives, however, need to be complemented by pull mechanisms that address the lack of market demand for neglected diseases products.

Pull programs provide certain key advantages. First, the financial reward would be only provided after successful product development. Moreover, the pull schemes are generally designed on a market-based approach that attract business-oriented companies and allows governments to redirect the innovative capacities of companies towards the product development of resource-poor countries. However, they need to provide a certain credibility of the sponsors to encourage investments of product developers. In addition, they might require structuring the mechanism in

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[270] *See* for example a recently adopted Recommendation of the European Commission with relevance for the European Economic Area (EEA) – C(2008)1329 – that seeks to provide Member States with policy guidelines for the development or updating of national guidelines and frameworks, and public research organizations with a Code of Practice concerning the management of IP and knowledge transfer. While it identifies the development of an IP policy as part of the long-term strategy and mission of the public research organization, and provides some principles concerning the exploitation, protection of IP and dissemination of knowledge, including the consideration of a "public domain" or "open innovation" approach or open-access publications of R&D results, it remains quiet in terms of the consideration of social or humanitarian aspects concerning, for example, resource poor countries and their related issues. Although a European recommendation is a non-binding legislative act for Member States, it has nevertheless, political force as an instrument that aims at the preparation of the national legislations in the countries. *See* European Commission Recommendation on the management of intellectual property in knowledge transfer activities and Code of Practice for universities and other public research organizations, Brussels 10.4.2008. At http://ec.europa.eu/invest-in-research/pdf/ip_recommendation_en.pdf, accessed on 10 August 2009.

a way that it also encourages competition and follow-on R&D and improvement of products.

Literature suggests the following pull schemes as potentially successful:

(1) Transferable patent term extension

A transferable patent term extension[271] would be awarded to a company that developed a neglected diseases product. The extension could be used for another existing (commercial) drug. This scheme would allow the right owner to capture additional economic benefits from the profitable product, which he could use to recoup R&D expenditure for the neglected diseases product[272]. The patent extension mechanism is currently applied selectively by the U.S. Food and Drug Administration through the pediatric exclusivity rule, which provides pharmaceutical companies with an additional six-month patent extension if they test their drug for pediatric use[273]. However, this model has been refused widely[274]. Granting rights over an unrelated product undermines one of the basic principles of the patent law that exclusivity rights are only provided for an invention that itself is the subject of the patent. Moreover, the scheme is designed to benefit MNC that are already proprietors of commercial valuable patents rather than SMCs or developing countries' firms. It provides a "the winner takes it all" mechanism that does not address im-

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[271] International Federation of Pharmaceutical Manufacturers associations (IFPMA), The pharmaceutical innovation platform – Sustaining better health for patients worldwide, 2004, p. 50;

Towse A., A review of IP and Non-IP incentives for R&D for diseases of poverty. What type of innovation is required and how can we incentivize the private sector to deliver it?, CIPIH submission 2005, pp. 7 ff [hereinafter Towse, 2005].

[272] In the United States the Elimination of Neglected Diseases Act of 2006 (S. 2699) proposed the introduction of a maximum two-year exclusivity extension in order to stimulate R&D for neglected diseases products. The initiative, however, has been rejected. At http://www.govtrack.us/congress/bill.xpd?bill=s109-2699, accessed on 10 December 2008.

[273] Pediatric Exclusivity under Section 505A of the U.S. Federal Food, Drug and Cosmetic Act. At http://www.fda.gov/opacom/laws/fdcact/fdcact5a.htm, accessed on 14 January 2008.

[274] CIPIH Report 2006, p. 103.

proved follow-on products. From the economic point of view it delays market entry of generic products resulting in higher costs for consumers of the commercial product or health insurances.

(2) Prize funds

The general idea of prize funds[275] is that sponsors (governments, public/private foundations) allocate a significant sum to reward the manufacturer of a new neglected disease product. The financial reward will be paid out in proportion to the health impact of the new health technology.

Various prize fund models are discussed and prize initiatives launched. A broad national approach applying a prize system is the U.S. Medicinal Innovation Prize Fund Act of 2007 (S. 2210), introduced to the U.S. Congress in October 2007[276]. The purpose of this bill is to provide incentives to encourage investments in R&D of new medicines through the establishment of a Medical Innovation Prize Fund and to enhance access to such medicines by allowing any person in compliance with regulatory authority requirements to manufacture, distribute, or sell an approved medicine. The Act proposes to allocate 0.6 percent of the U.S. gross domestic product for rewarding innovative health R&D. Developers of health technologies would be directly rewarded on the basis of incremental therapeutic benefit to consumers as compared to existing drugs. Criteria for determining the amount of prize payments also include considerations such as the degree to which the health product addresses priority health care needs, for example global infectious diseases or ne-

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[275] Hollis A., An optimal reward system for neglected diseases drugs, 2005, pp. 1-23; Stiglitz J.E., Scrooge and intellectual property rights, BMJ, December 2006, p. 1279; Crager S.E., Price M., Prizes and Parasites: Incentive models for addressing Chagas Diseases, Journal of Law, Medicines and Ethics, Vol. 37:2, 2009, p. 292 – 302; Abramowicz M., Perfecting patent prizes, 2003, pp. 1 ff. At http://www.law.gmu.edu/assets/files/publications/working_papers/01-29.pdf, accessed on 10 December 2008; Love J., Hubbard T., The big idea: Prizes to stimulate R&D for new medicines, Symposium: Intellectual Property, Trade and Development: Accommodating and Reconciling Different National Levels of Protection, Chicago-Kent Law Review, Vol. 82, No. 3, 2007, pp. 1520-1554.

[276] U.S. Medicinal Innovation Prize Fund Act of 2007 (S. 2210), introduced to the U.S. Congress in October 2007. At http://www.govtrack.us/congress/bill.xpd?bill=s110-2210, accessed on 10 December 2008.

glected diseases that primarily affect the poor in developing countries. The legislative initiative further proposes the elimination of exclusivity rights to market drugs and biological products (Section 5) and to replace the remuneration through exclusivity profits by payments from the established Fund. Eliminating legal monopolies would allow for generic competition resulting in lower prices for health products thus reducing barriers to access.

A global and more focused approach of a prize system is the "Prize for the Development of New Treatments for Chagas Diseases", as one of five different medical innovation prize programs presented by Barbados and Bolivia during the meeting of the WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property in May 2008[277]. It addresses the development of new treatments for Chagas diseases and asks the WHO and governments to put in place a $ 250 million prize fund to reward, among others, new treatments that improve health outcomes for the populations at risk and "best contributions" to the scientific and engineering know-how needed for new treatments. The proposal also includes the creation of a licensing pool and requires the winner of the prize to grant reasonable non-discriminatory licenses to all patents and know-how needed for competitive supply of the technologies. A last example of prize programs is the recently launched Health Impact Fund (HIF). The manufacturer of a new pharmaceutical product with marketing approval would have the opportunity to choose either to follow on the business model of patent exclusivity and charging higher (monopoly) prices, or registering the product with HIF. In the case of registration, the manufacturer would be required to provide the drug

[277] All proposals can be found at http://www.keionline.org/index.php?option=com_content&task=view&id=4, accessed on 11 December 2008. They include 1) Prize Fund for Development of Low-Cost Rapid Diagnostic Test for Tuberculosis; 2) Prize for the Development of New Treatments for Chagas Diseases; 3) Priority Medicines and Vaccines Prize Fund (PMV/pf), to be set up to stimulate the development of medicines and vaccines for Type II and III diseases, new antibiotics and emerging public health threats; 4) Prizes as Reward Mechanism for New Cancer Treatments, focusing on cancer in developing countries; 5) Licensed Products Prize Fund (LP/pf) for Donors, a potential solution for donor-supported market that links rewards for R&D to a voluntary participation in licensing the competitive supply of products for HIV/AIDS, tuberculosis, malaria and other humanitarian uses.

worldwide at an administered price near the average cost of production and distribution in exchange of payments from the HIF, based on the assessed global health impact of the product[278]. The HIF program, in contrast to other prize models, does not require changes to the patent or licensing system[279].

All three examples intend to provide alternative or additional mechanisms to the current patent incentive model to stimulate pharmaceutical R&D that focuses on products that improve health care outcomes and that is directed to areas with greatest needs. The underlying theory of the prize programs is to de-link the reward for successful R&D from the price of the product thus facilitating access to the technologies, including for patients in developing countries with little purchasing power. Drug or vaccine developers could recoup the R&D costs from the prizes provided by the funds instead of higher product prices enabled by patent exclusivity.

The models are additionally set up to reward only successful product development in terms of health benefits they provide. The remuneration would be provided proportionally to the incremental health benefits that the new health tools offer. Products for neglected diseases may be expected to provide significant incremental benefits in comparison with most other drugs in consideration. Under the current patent-based system only one third of the drugs approved by the FDA in the United States during the time period from 1989 to 2000 were based on new "molecular entities" that treat diseases in novel ways, while the other products represent no real therapeutic advance over the existing ones[280]. A reward for innovation based on the extent of global health benefit is expected to stimulate the development of innovative health tools with the

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[278] Hollis A. and Pogge T., The Health Impact Fund: Making new medicine accessible to all, Incentives for Global Health, 2008, Executive summary, p.1. At http://www.yale.edu/macmillan/igh/#, accessed on 11 December 2008.

[279] *Ibid.*, p.16.

[280] National Institute for Health Care Management (NIHCM), Changing patterns of pharmaceutical innovation, 2002, p. 3. Available at http://www.nihcm.org/~nihcmor/pdf/innovations.pdf, accessed on 7 August 2009.

highest potential for public health impact. Thus, a prize fund could be an incentive to reallocate R&D expenditures to neglected diseases and achieve a better balance between used financial resources for R&D and health priorities, however, without the "inefficiencies associated with monopolization"[281]. Funding for the prizes in the case of diseases affecting resource-poor countries may be provided from the Official Development Assistance budget of countries[282].

Last, the prize fund could be designed in a way that would allow to immediately place knowledge into public domain, facilitating open access to knowledge and permitting generic competition to reduce product prices, while maintaining incentives for innovation[283].

The main difference between the three designs, however, is the handling of intellectual property. While the Medicinal Innovation Prize Fund Act is being hostile to exclusivity rights and advocates the prize fund as alternative to the patent system, the second proposal by Barbados/Bolivia is opting for a solution on the licensing side to ensure access to innovation. The third model, the HIF initiative, is an optional system, leaving it to the developer of a product to choose. The various ways to design a prize fund will influence its attractiveness to potential drug developers, as well as donors. A radical change of the incentive system of intellectual property is rather unlikely under current political climate and innovation policy, making proposals such as the Medical Innovation Prize Fund difficult to promote. Attractive prize fund designs would have to address, among others, issues such as stability and credibility of the fund, payment administration, i.e. size, timing and predictability of the awards,

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[281] Stiglitz J., Give prizes not patents, New scientist, 2006, p. 21.

[282] Stiglitz J., Prizes, not patents, Commentary, Project Syndicate, 2007. Available at http://www.project-syndicate.org/commentary/stiglitz81, accessed on 10 August 2009.

[283] Love J., Drug development incentives to improve access to essential medicines, Bulletin of the World Health Organization 84, No. 5, 2006, pp. 408-411.

One example of an access to knowledge clause is provided in the Barbados and Bolivia proposal on a Chagas Disease Prize Fund for the development of new health tools. The document includes an incentive mechanism for collaboration and access to knowledge. Ten percent of the prize money would be given to scientists and engineers that openly published and shared the most useful research, data materials and technology. *See* footnote 275.

and the fair and transparent rules and procedures to determine the winner. The definition of appropriate evaluation methods to determine the health impact of the developed product as basis for payments from the fund is another key issue.

(3) Advanced Purchase Commitment (APC)

Sponsors commit in advance to fully or partially finance the future purchases of a neglected disease product (in development) at a predetermined price. The health tool would have to meet pre-specified standards, such as efficacy and safety, and be demanded by developing countries[284]. These countries would decide whether to purchase a product at a low and affordable price, and sponsors guarantee to replenish up to the predetermined price thus providing returns comparable to other products. The form of the commitment would be a contract to be signed by the sponsors and preferably enforceable by contract law and existing legal institutions in order to guarantee credibility of the undertaking[285]. Contractual arrangements would also include commitments of the developer to sell the product at an affordable price once the guarantee of the sponsors expires.

APCs intend to replicate valuable markets for neglected diseases products and reduce some of the economic risks developers can be confronted to in developing countries' markets for pharmaceutical products. In the same way as for the prize schemes, they also only reward successful R&D. Access to new health technologies is supported by the higher pre-defined purchase price and after expiration of the guarantee by the contractual commitment of the developer to provide the health tools at low price.

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[284] Berndt E.R., Glennerster R., Kremer M.R., Lee J., Levine R., Weizsäcker G., Williams H., Advanced market commitments for vaccines against neglected diseases: Estimating costs and effectiveness, National Bureau of Economic Research (NBER) working paper 11288, 2005, pp. 5 ff; Towse A., Kettler H., Advanced price or purchase commitments to create markets for treatments for diseases of poverty: lessons from three policies, Bulletin of the World Health Organization, April 2005, 83 (4), p. 303 [hereinafter Towse and Kettler, 2005].

[285] Towse, 2005, p. 81.

Key issue of the APC is, as also described for the prize fund systems, the design of the contractual agreement. Some features may be problematic: the establishment of financial and contractual credibility of the commitment given the long product development time of pharmaceuticals of more than 10 years; the challenge to preset the price at a level that encourages pharmaceutical companies to invest in R&D; the predetermination of the quality specifications that may require to include additional factors particularly related to health infrastructure and needs of developing countries; the way to consider subsequent entrants in the case that more than one qualifying product has been developed or in the case of improved follow-on products; and lastly, provisions to ensure delivery and use of the product purchased under the APC when considering the difficult health environment in developing countries related to political, logistical and capacity issues[286]. Main critics of the APC have expressed the concern that it is not sufficient to stimulate R&D in neglected diseases products that are at the early stage of the innovation process. Given the high scientific and market uncertainty and low profitability opportunities involved in pharmaceutical R&D for diseases of the poor, incentives offered by the APC are unlikely to redirect the R&D focus of (multinational) pharmaceutical companies to neglected diseases, putting aside more potentially profitable market segments. APCs are seen as better suited for late-stage development products close to be marketed and as incentive that may take potential product candidates with strong possibility of success through the last innovation stages of clinical trial, marketing and delivery[287].

Leaving the level of academic theory and discussion on feasibility and cost-effectiveness, the APC model has been turned into a real life experiment. A pilot APC has been announced for pneumococcal vaccines in February 2007. Contributors are the governments of Canada, Italy, Norway, the Russian Federation, The United Kingdom and the Bill & Melinda Gates Foundation. The commitments range around U.S. $ 1.5

[286] Towse and Kettler, 2005, p. 305.

[287] CIPIH Report, 2006, p. 105.

billion. The Global Alliance for Vaccines and Immunization (GAVI) and the World Bank are responsible for supporting the programmatic and financial functions of this APC[288]. Funds are provided to subsidize the purchase at a pre-agreed price of a not-yet-available pneumococcal vaccine, if developed in pre-determined quantities and if demanded by GAVI countries. The pilot APC also includes the provision that participating companies will provide the vaccine at lower price for a period of time after the expiration of the APC subsidies.

The APC is directed at a global disease occurring in industrialized and (L)DCs. Although it addresses "not-yet-developed" pharmaceutical products, it appears to support vaccine development projects already performed, such as at the pharmaceutical company GlaxoSmithKline with a pneumococcal vaccine candidate in late-stage development[289]. Nevertheless, it may provide important evidence whether the APC model will likely be effective as mechanism for other interventions.

(4) Transferable fast track or priority review approval

The transferable fast track or priority review approval of regulatory authorities awards the developer of a new neglected diseases product by a fully transferable right of fast track or priority review of the regulatory authority for another pharmaceutical product of his choice. The underlying rationale of the scheme is that a faster market approval of a potentially commercial product will provide an extended patent protected marketing period for the chosen product thus the opportunity to gain additional profits. Estimates suggest that the time reduction would be worth U.S. $ 300 million for a potential blockbuster drug[290]. Increased re-

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[288] Webpage of the GAVI Alliance, Five nations and the Bill & Melinda Gates Foundation launch Advance Market Commitment for vaccines to combat deadly disease in poor nations. At http://www.gavialliance.org/resources/7___Advanced_Market_Commitment.pdf, accessed on 12 December 2008.

[289] GlaxoSmithKline commends $ 1.5 billion advance market commitment for vaccines, Press release, London, 9 February 2007, at http://www.gsk.com/media/pressreleases/2007/2007_02_09_GSK973.htm, accessed on 12 December 2008.

[290] Ridley D.B., Grabowski H.G., Moe J.L., Developing drugs for developing countries, Health Affairs 25 (2), 2006, pp. 313, 314.

turns could recoup a significant portion of the cost for the neglected diseases product development. This mechanism has become law in the United States, where the Priority Review Voucher (PRV) has been included into the 2007 Food and Drug Administration Act under Section 524 to encourage the development of treatments for tropical diseases[291]. A PRV provides the opportunity of a faster six-month review of one new drug submitted to the Food and Drug Administration (FDA) instead of following the FDA standard procedure of ten months. The voucher is fully transferable. It will be awarded to a developer upon approval of a tropical diseases product application. "Tropical diseases" are defined in a statute list[292]. Other infectious diseases are also included, for which there is no significant market in industrialized nations, if they disproportionately affect poor and marginalized populations and are designated by regulation. To use the PRV, the developer must pay a special priority review user fee that will be established by the FDA each fiscal year. As a program implemented into the regulatory process, the PRV requires no up-front financial outlays by the government, meaning no additional costs for consumers or tax payers, and no budgetary regulations[293]. It nevertheless has been received with ambivalent reactions. Priority approval is intended for those products that address unmet medical needs[294]. Main critics argue that priority reviews for products that oth-

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[291] Section 1102 Priority Review to encourage treatments for tropical diseases, Food and Drug Administration Amendment Act of 2007 (H.R. 3580), signed into law on 27 September 2007. At http://www.fda.gov/oc/initiatives/HR3580.pdf, accessed on 12 December 2008.

[292] The statute list: tuberculosis, malaria, blinding trachoma, buruli ulcer, cholera, dengue/dengue haemorrhagic fever, dracunuliasis (guniea-worm disease), fascioliasis, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis, soil transmitted helmithiasis, and yaws, *see* Section 524 (a) (3) of the new U.S. Food, Drug and Cosmetic Act of 2007.

[293] International AIDS Vaccine Initiative, US FDA priority review vouchers: An effective incentive to develop drugs and vaccines for neglected diseases?. Available at https://www.iavi.org/Lists/IAVIPublications/attachments/2753fdcb-a273-4f09-b65a-63a34f9c283d/IAVI_US_FDA_Priority_Review_Vouchers_An_effective_incentive_to_develop_drugs_and_vaccines_for_neglected_diseases_2008_ENG.pdf, accessed on 12 December 2008.

[294] In the United States, the accelerated registration is basically allowed for drugs for serious and life-threatening diseases, and for a limited number of commercial diseases, such as diabetes and obesity. FDA homepage, at http://www.fda.gov/ForConsumers/ByAudience/

erwise would not receive fast track review would take away human resources from reviewing applications that deserve the faster marketing approval[295]. Moreover, in contrast to model proposals such as the prize fund or the APC, the value of the PRV is not linked to the usefulness of the developed health technology it intends to reward[296]. Products that are less adapted to developing country needs and infrastructure environment, for example because of delicate stocking requirements or difficult modes of administration, may also receive a PRV. The first use of the PRV mechanism has displayed another short-coming of the incentive: one pharmaceutical company has applied for market approval in the United States for its anti-malaria drug based on an artemether/lumefantrine combination developed in the 1990ties[297]. Since 2001, the company has provided more than 190 million treatments to developing countries and the product is included on the WHO Model Lists of Essential Drugs[298]. With the market approval for the already intensively used malaria drug, the firm may receive a PRV that originally has been created with the intention to stimulate and reward new drug development. The use of the PRV incentive scheme by pharmaceutical developers for existing and delivered products allows companies to benefit from the provided reward without essentially contributing to new R&D efforts for urgent public health need, thus undermining the basic principle of the incentive mechanism.

ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm#accelerated, accessed on 15 December 2008.

[295] Spatz I.D., Vouchers for FDA Priority Reviews, Health Affairs, Vol. 25, No. 4, July/August 2006, p. 1184.

[296] Kesselheim A.S., Drug development for neglected diseases – The trouble with FDA Review Vouchers, NEnglJM, November 2008, p. 1981.

[297] According to email correspondence from Novartis to Oxfam International on October 14, 2008, the decision to apply for FDA approval of the anti-malaria drug (Coartem) has been made prior to enactment of the law introducing the PRV. Novartis has not discussed with the FDA whether its drug qualifies for the program and does not know if it qualifies, but the company assumes it would if Coartem receives market approval. *See* Oxfam Briefing Paper No. 122, Ending the R&D crisis in public health: Promoting pro-poor medical innovation, Oxfam International, November 2008. At http://www.oxfam.org/policy/ending-r-and-d-crisis-public-health, accessed on 8 January 2009.

[298] Novartis Brochure, A committed partner in the fight against malaria.

(5) Patent buy-outs

Under the proposal of patent buy-outs, donors and governments acquire the patent and exclusive marketing rights for an essential medical invention from the patent owner (with the possibility to limit it to a particular geographical market). The patent is then offered to generic manufacturer as open, non exclusive, no royalty license (for sale in the targeted market)[299].

Patent buy-outs provide certain advantages in comparison to other mechanisms. First, they separate the market for innovation from the market for the health product. From the economic point of view, patents placed in the public domain allow the widest possible distribution of the invented product at the lowest market price[300]. In addition, the patent buy-out offers the opportunity of free competition in manufacturing the drug without the need to previously defining the specifications of the product as implied for schemes such as the APC.

Drawbacks of the mechanism include the difficulties in estimating and determining the buy-out price. Various models to set the price are discussed. Proposals include an auction mechanism[301], or price setting based on the calculation of expected future profit[302]. Another shortcoming is the downside of the free manufacturing competition advantage. The patent buy-out model is not linked to the quality of a developed product, and hence allows for less control on the research output.

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[299] Outterson K., Patent buy-outs for global disease innovations for low- and middle-income countries, American Journal of Law and Medicines, 2006 [hereinafter Outterson, 2006], pp. 159-173.

[300] *Ibid*.

[301] Kremer M., A mechanism for encouraging innovation, The Quarterly Journal of Economics, Vol. 113 (4), 1998, p. 1146.

[302] Outterson, 2006.

(6) International Medicinal R&D Treaty

The basic idea of the International Medicinal R&D Treaty proposal[303] is that participating States commit to spend a certain percentage of the national gross product on medical R&D, such as basic research, R&D of pharmaceutical drugs, vaccines and diagnostic tools, or the preservation and dissemination of traditional medicine knowledge. The treaty seeks to "create a new global framework for supporting medical R&D that is based upon equitable sharing of the costs of R&D, incentives to invest in useful R&D in the areas of need and public interest, and which recognizes human rights and the goal of sharing in the benefits of scientific advancement"[304]. The main objective is the promotion of a sustainable system of medical innovation that will, among others, identify priority areas of R&D, fairly allocate the costs of supporting medical R&D, encourage the broad dissemination of information and sharing of knowledge, and equitable access to useful medical inventions. The obligation of each party increases with per capita national income, thus distributing the responsibility of supporting R&D equitably. Parties to the treaty are free to decide on the way to devote the required financial contributions to the qualified R&D projects. They can do this for example, in form of push schemes such as direct funding or tax credits and/or by using pull mechanisms, such as purchases of medicines, royalty payments to patent owners, or innovation prizes. A minimum share of the financial contribution would have to be allocated to priority research targets, including vaccine development, neglected diseases or global infectious diseases. The treaty also creates a novel credit system, similar to the Kyoto Protocol[305], to reward exceptional productive and useful projects, for example in the area of open research, technology transfer, or R&D for priority research projects, such as neglected diseases. The credits would be tradable and could be used to fulfill treaty obligations of parties to the treaty. Moreover, as core element, the treaty regulates that members "agree to

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[303] Consumer Project on Technology, at http://www.cptech.org/workingdrafts/rndtreaty4.pdf, accessed on 16 December 2008.

[304] *Ibid.*, Preamble of the draft text, p. 2.

[305] Kyoto Protocol to the United Nations Framework Convention on Climate Change, 1998.

forgo certain WTO TRIPS dispute resolution cases, or bilateral or regional trade sanctions, in areas where compliance with the terms of the Treaty provides an alternative and superior framework for supporting innovation."

The treaty draft has been presented to the WHO in 2005, including the signature of more than 160 medical researchers, non-governmental organizations, parliamentarians, government officials, and other stakeholders asking the WHO to evaluate the proposal of a global R&D treaty framework[306].

The advantage of the Treaty proposal is the long-term commitment of governments to R&D funding that would create sustainable sources in the field of medicinal R&D financing. The more centralized government led system of R&D, as proposed in the treaty draft, however, has certain shortcomings. The setting up of such a system that specifically seeks to replace the current market-based patent incentive scheme for pharmaceutical R&D is particularly concerning. Governments may decide differently on research priorities than private sector companies responding to consumer needs, which may lead to the result that consumer innovation that does not comply with the authority preference will not be funded. Furthermore, once programs have been initiated, it will be difficult to terminate inefficient and costly projects due to domestic job market and other political considerations. The replacement of a high proportion of the private R&D investments by public ones may also lead to strong protectionist motives as key drivers of a State's R&D funding contribution and politicization of funding allocation, both factors that may lead to large inefficiencies in R&D productivity[307].

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[306] Consumer Project on Technology, at http://www.cptech.org/workingdrafts/rndtreaty4.pdf, accessed on 16 December 2008.

[307] DiMasi J.A., Grabowski H.G., Patents and R&D incentives: Comments on the Hubbard and Love trade framework for financing pharmaceutical R&D, June 2004, pp. 6, 7.

c) Public-private partnerships for product development

As described above, the reaction on market failures, such as the lack of pharmaceutical products for neglected diseases, is to introduce or enhance push and pull incentives for the private sector in order to increase investments in the needed field. International discussions focus on finding commercial mechanisms that are valuable enough to stimulate MNCs' interest for the unprofitable area of diseases in resource-poor countries. According to an often cited study, however, the majority of neglected disease drug development is performed outside the current commercially incentivized business model of the pharmaceutical industry[308]. Much of the R&D effort that has been initiated in the last years was carried out by private sector companies alone or in collaboration within so-called public-private partnerships (PPP) or public-private partnerships for product development (PDP), and occurred without significant incentive mechanisms in place. The industry's main motivations to get involved in the neglected diseases R&D field in collaboration with PDPs are long-term business considerations rather than financial returns in neglected diseases markets. Company's contributions are developed under Corporate Social Responsibility considerations, or include motivational factors such as reputational gains from addressing developing country needs, business strategies to define a market position in emerging developing countries, such as Brazil or India, and having access to high-skilled and low-cost research environment in these countries[309].

The study demonstrates a significant increase in R&D activities in the neglected diseases field since the beginning of the 21st century. The alternative model of PPPs/PDPs was described as the driving force for most of the ongoing neglected diseases R&D projects[310]. PPPs/PDPs emerged in the late 1990's after it became apparent that the traditional for-profit market model of MNCs would not contribute to the product development for developing countries needs. Stakeholders developed an alterna-

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[308] LSE Report, 2005, p. 12.

[309] LSE Report, 2005, p.11.

[310] LSE Report, 2005, p. 8.

tive scheme, the PPP/PDP model, that tries to integrate the skills and capacities of the various actors involved in the pharmaceutical R&D. PPPs in the field of neglected diseases are arrangements between various stakeholders, including, for example, academia, pharmaceutical and biotechnology companies, philanthropic foundations and governments. The term "public-private partnership" is often used to describe both the public-private partnering as an activity (functional definition) and public-private partnerships for product development (PDP) as a formal organization (structural definition). The former refers to multiple activities, including for example drug donations or partnerships with public and private organizations working together on a common R&D project. The structural definition encompasses formal organizations such as product development partnerships formed to perform neglected diseases R&D, for example the Drugs for Neglected Diseases initiative (DNDi)[311], the iOWH[312] or the Foundation for Innovative New Diagnostics (FIND)[313]. These organizations are single entities that collaborate with many partners. The collaborations may constitute a public-private partnership under the functional definitions but do not create a new formal organization under the structural definition[314]. An example is the above mentioned Oxford University Tuberculosis vaccine case (chapter C II.1.) where the collaboration between the PDP Aeras Global TB Vaccine Foundation and the other partners, such as the donors, form a public-private partnership according to the functional definition.

Drug development partnerships for tropical infectious diseases have already been successfully established by the Special Programme for Research and Training in Tropical Diseases (TDR)[315]. The Organization was

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311 http://www.dndi.org/

312 http://www.oneworldhealth.org/

313 http://www.finddiagnostics.org/

314 Moran M., Ropars A.-L., Guzman J., Partnership dynamics, issues and challenges, Global Forum for Health Research, Update on Research for Health, Volume 4, 2007, p. 140.

315 For an overview of the TDR history *see* TDR, Making a difference – 30 years of research and capacity building in Tropical diseases, 2007. Available at http://apps.who.int/tdr/svc/publications/about-tdr/30-year-history, accessed on 11 August 2009.

founded in 1975 by the United Nation's Children Fund (UNICEF), the United Nations' Development Programme (UNDP), and the World Bank at the WHO. Following its core mission of fighting tropical diseases, it was significantly involved in the development of some of the few new pharmaceutical products approved specifically for treating neglected infectious diseases such as leishmaniasis or African trypanosomiasis, or onchocerciasis, in partnership with a variety of public and private key players in the pharmaceutical R&D sector[316]. TDR also played a significant role in the creation of some of the formal public-private partnership organizations, the PDPs such as Medicines for Malaria Venture (MMV), the Global Alliance for TB drug development, DNDi and FIND[317].

The shared feature of PPPs (including the formal organizations PDPs) is to join funding and expertise from all stakeholders. The rationale is that "none of the individual players – the public sector and academia, the pharmaceutical industry, the biotech sector, contract research organizations (CROs), or the non-profit organizations – have the skills and resources necessary to discover and develop products which are needed by millions of people but for which there is no commercially viable market"[318]. Successful product development for neglected diseases requires highly specialized know-how, experienced project management, large investments and funding and multiyear commitment[319].

In such a framework, it is the task of the public sector to facilitate the development of health tools by, for example, subsidizing clinical trials,

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[316] With input from TDR, eight drugs for neglected diseases were developed and registered. LSE Report, 2005, pp. 46, 48.

[317] Within the changed landscape of neglected diseases R&D, the Organization will maintain its product discovery and development activities on neglected priority areas that are not sufficiently addressed by the newly involved stakeholders. However, it will include empowerment (fostering of research capacities in developing countries) and stewardship (harmonizing support and aligning research to country needs) into its health and R&D related activities. *See* TDR Webpage, at http://apps.who.int/tdr/, accessed on 10 August 2009.

[318] Consultation document 2009, citing Croft S.L., Public-private partnerships: from there to here, Transactions of the Royal Society of Tropical Medicine and Hygiene, 2005.

[319] Consultation document, 2009, citing Matter A., Keller T.H., Impact of non-profit organizations on drug discovery: opportunities, gaps, solutions, Drug Discovery Today, 2008, pp. 347-352.

providing public health knowledge related to neglected diseases, and facilitating the registration process. Academia is important at the first stage of the product development process; it performs the research into the mechanisms of a disease and provides much of the ideas and knowledge for the further steps. The role of the pharmaceutical companies is to translate this knowledge into safe and effective health products. PPPs/PDPs integrate the product development process across multiple partners and/or subcontractors from the private sector, academia and others and act as fund managers, resource allocators, and portfolio managers. As such they are "bridging commerce and philanthropy and are applying market-driven models to humanitarian initiatives"[320].

The emergence of the PDPs had a significant impact on R&D for the neglected diseases affecting populations in resource-poor countries. The number of research projects undertaken worldwide in this therapeutic area has increased substantially. One part of the research endeavors are performed by MNCs alone or in partnership within PPPs, or with PDPs, for the above mentioned reasons. They conduct the research under a not-for-profit approach (or "no profit-no loss") by focusing their investments on early-stage R&D and/or by entering into PPPs or collaborations with PDPs for the more expensive clinical development, product registration and distribution in developing countries[321]. Some other projects are carried out by smaller companies and academic institutions reimbursed by a PPP/PDP for their R&D contributions, or by small firms alone with a commercial interest to exploit the developing country market[322]. The number of MNCs R&D activities in the field of neglected diseases and

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[320] Consultation document, 2009, citing Croft S.L., Public-private partnerships: from there to here, Transactions of the Royal Society of Tropical Medicine and Hygiene, 2005.

[321] LSE Report, 2005, p. 13.

[322] The LSE Report (2005) identified 63 R&D projects for neglected diseases. 32 research projects were conducted with pharmaceutical industry participation, with more than half of them running under the auspice of PDPs. This figure includes R&D projects for malaria, Tuberculosis and other tropical diseases. 29 projects were carried out by small and medium-sized companies, developing country firms and academic institutions or contract research organizations. See LSE Report, 2005, p. 10.

the number of collaborations with not-for-profit organizations has continuously increased within the last years[323].

PDPs have been described as the strongest "push-program" for the development of products for neglected diseases. They are public health driven not-for-profit virtual entities. The organizations are mainly sponsored by private donors such as the Bill and Melinda Gates Foundation, the Rockefeller Foundation or by contributions of groups, such as Médecins Sans Frontières, while funding from OECD governments collectively represents less than 20 percent of the PDPs' budgets[324]. Key inputs of the not-for-profit organizations are the direct research funding they provide to their partners and the developing country expertise, particularly the technical skills to perform clinical trials in developing countries, as well as to deliver developed products to these regions. Both factors result in minimizing the cost and risk of the R&D performance ("no loss") of pharmaceutical companies and allows them to produce and deliver safe, efficient, and developing country adapted health products to patients in need at "no profit" prices[325]. Main advantages of the PDPs are their significant cost effectiveness in product development and use of public funds[326], and their creative intellectual property policy approach ensuring that health technologies are affordable and accessible for patients in

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[323] The first data on the number of projects of the pharmaceutical industry was published in the LSE Report in 2005, p. 10.

According to the latest status report of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), pharmaceutical companies are currently involved in 75 projects for product development for neglected diseases as prioritized by TDR. 66 of these endeavors are carried out in partnership with PDPs, and 18 programs are industry alone projects. Of the 75 R&D programs, 22 are for tuberculosis, 30 for malaria and 23 for other tropical diseases. *See* IFPMA Status Report, Pharmaceutical industry R&D for diseases of the developing world – 2009, July 2009, p. 1. Available at http://www.ifpma.org/fileadmin/pdfs/webnews/2009_07_07_Status_RnD_for_DDW_07Jul09.pdf accessed on 11 August 2009.

[324] LSE Report 2005, p. 33.

[325] *Ibid*., pp. 13, 14.

[326] LSE Report 2005, pp. 58 ff, *see* also table 6 of the Report, providing examples of R&D costs for selected projects, p. 61; Nwaka S. Ridley R.G., Virtual drug discovery and development for neglected diseases through public-private partnerships, Nature Review Drug Discovery, Vol. 2, November 2003, p. 926.

developing countries[327]. Moreover, in their role as fund allocator, they reduce governments' risk in choosing the optimal R&D projects, also by distributing the funds to a variety of projects instead of subsidizing individual projects[328]. Additionally, the PDP focus on neglected diseases and (L)DC public skills appear to support the development of optimal health tools adapted to their environments and patients needs[329]. They also manage to involve SMCs into the R&D process for neglected diseases.

One of the first pharmaceutical products developed under the PDP business model is the Paromomycin IM Injection for the treatment of visceral leishmaniasis of the iOWH[330].

The key issue, however, is the lack of sustainable and sufficient funding. This impedes the organizations' ability to establish contracts with private sector partners and delays research projects. Moreover, PDPs' neglected diseases R&D endeavors that are at the preclinical or early clinical stage will reach the clinical development. Thus, they require heavily increased investments that will, however, have to be leveraged, also for new emerging projects. Additionally, PDPs reliance on philanthropic funding and the goodwill of donors makes this approach less sustainable and questions the suitability of PDPs as long-term solution to provide needed health tools for developing countries. The dependency on the few philanthropic sources may, furthermore, shift control of R&D focus and project management factors, such as time line, to major donors, or may leave R&D areas that are not in the interest of the funders underserved. To ensure the sustainability and the independence of PDPs, and their per-

[327] An example is the DNDi agreement with the pharmaceutical company sanofi-aventis: The company will manufacture a fixed-dose artesunate-based combination for malaria developed by DNDi, artesunate-amodiaquine, on a non-exclusive basis and make it available to governments of disease endemic countries, non-governmental organizations and international organizations at less than a dollar per adult treatment and less than 50 cents per pediatric treatment. At http://www.dndi.org/press-releases/458-sanofi-aventis-and-dndi-enter-into-a-collaboration-agreement-on-a-new-drug-for-sleeping-sickness-fexinidazole.html, accessed on 16 December 2008.

[328] LSE Report, 2005, p. 37.

[329] LSE Report, 2005, pp. 52 ff, and p. 64.

[330] Institute for OneWorldHealth webpage, at http://www.oneworldhealth.org/leishmaniasis, accessed on 16 December 2008.

formance continued in the R&D process it will be vital to broaden the funding perspectives of PDPs in terms of both increased funding, particularly by governments, and the variety of sponsors.

The support to neglected diseases product development, particularly performed by PDPs, is important as a short- and medium-term goal to address the prevailing neglected diseases affecting resource-poor countries.

III. Final remarks

There are, in general two different types of programs that can be implemented by governments and the international public health community to foster R&D for neglected diseases. As described above, push programs reward research inputs, and pull programs the research outputs. Both program systems hold attractive incentives that provide advantages, however, also major drawbacks.

Push incentives require upfront commitment of the governments to the recipients. This may cause the problem of deciding on the best option or project, for example, if funding grants are to be provided. There is no guarantee for success, i.e. that a suitable product will be found for a particular disease. In some cases, push programs may not incentivize research adapted to developing country needs. Proposals including the regulatory process, for example a fast track procedure, are by themselves unlikely to increase the amount of research. Nevertheless, they can be a positive addition that supports particularly smaller companies.

The promotion of **patent pools** in the field of neglected diseases and social licensing programs, especially of public research institutions, can provide interesting policy options for governments. For the former program scheme, a certain willingness of the pharmaceutical industry has been manifested. Fostering and implementing humanitarian or **social licensing**, however, could find stronger emphasis in the policy considerations of public research institutions, the pharmaceutical industry and

governments. In particular, such programs could provide an opportunity to use the highly disputed IPR tools in a creative way and favorable for (L)DCs public health needs.

Pull programs for neglected diseases R&D intend to address the lack of a valuable market in endemic countries. Provided only after successful product development they are generally assumed to be less risky. Nevertheless, they are also more cost intense and require careful weighing of advantages and disadvantages. Depending on the motivations and priorities of donors and governments, as well as the disease to be addressed, it might be in each case another program that prevails. Decisive factors may vary and include, for example, cost effectiveness of the incentive, the credibility it provides to the product developer, but also political considerations of governments to support local industry by implementing nationally or contributing to one international structured program.

Some pull models allow for price setting and product specifications in advance (**APC**, **prize funds**), i.e. they create a link between payments and product quality. Defining the features of the desired products and the price in advance, in turn, provides also one of the major challenges inherent to the programs. Both the APC and the prize fund for a neglected disease must be designed to address the case of multiple qualifying products, and, in addition, to foster competition for subsequent improvements. The main drawback of both programs is that they require significant upfront investment of the firms for the product development. This may mean that promising projects cannot be started, even with the perspective of a significant award after successful realization. It makes the schemes less suitable for smaller companies that may not be able to provide the high product development costs in advance or to find (venture capital) investors to perform the R&D for a neglected disease. Getting multinational companies' involvement, however, may require significant governments' and donors' investments that are sufficient to simulate an interest.

Proponents of the **prize fund** or the **patent buy-out** emphasize as particular advantage of the models the waiver of exclusivity rights conferred by patents that would ensure sustainable, affordable and timely access to the developed health tools in resource-poor countries.

The **Priority Review Voucher** (PRV) could be implemented at low cost for governments. Although it will be rather unlikely that the program for itself will encourage R&D for neglected diseases, it can nevertheless be a positive complement to other incentives.

Some of the proposals, such as the Medicinal **R&D Treaty** and the Medical Innovation Prize Act of 2007, address the weaknesses of the current patent-based incentive model in general, as well as in the case of neglected diseases R&D, and intend to provide an alternative or to replace the system. Radical changes of this scope, however, are rather unlikely to take place.

Other pull programs are already implemented, such as the PRV in the United States, or the APC for pneumococcal vaccine. They will serve as models for further interventions and development of mechanisms to foster pharmaceutical innovation for neglected diseases.

However, none of the programs alone is suitable to stimulate R&D performance for neglected disease form the discovery stage until the late stages of clinical trial and marketing. A combination of continued push funding complemented by the implementation of pull financing mechanisms may be a possible strategy to foster the drug development for neglected diseases, and a strategy that stays within currently existing paradigms and approaches to address market failures.

One policy option would be to use the various orphan drug regulations (ODRs) as framework to implement incentives for neglected diseases. For this, some of the provisions and stimulus programs could be adapted to the features of the tropical diseases, for example, by broadening the rules for the assignment of the "orphan" status to also include diseases that are prevalent in (L)DCs; or, by implementing other pull incentives than the market exclusivity, such as the APC or a prize fund, in order to address failing markets in resource-poor countries.

A neglected disease drug developer would then be entitled to all push incentives provided in the orphan drug regulations, such as tax credits, grant programs, or protocol assistance during the regulatory process. The latter may be of particular importance because of the difficulties in organizing and performing clinical trials in developing countries due to the resource constraints in these regions. A drug developer would also be enabled to benefit from enhanced pull incentives provided in an adapted ODR.

The efficiency of the implementation of neglected diseases into the ODRs, however, is questionable. The lack of pharmaceuticals for neglected diseases is a global health problem, and ODRs are designed as a single country approach. Most of the commercial pull incentives discussed for neglected diseases R&D, such as the prize fund or the APC, require a concerted commitment of several donors and governments due to the amount of finances that are needed. Moreover, stakeholders involved in neglected diseases R&D perform important research steps in the endemic regions outside the ODR countries; often stakeholders from various countries are involved in the same innovation process. A national legislation, such as the ODR, may not be flexible enough to address the internationality of the neglected diseases issue. In addition, it might be politically difficult to promote the implementation of diseases not endemic in the individual country, or region, as it is the case with the European ODR, as well as to provide the required financial resources for the incentive mechanisms.

Another policy option would be to use the various push and particularly pull programs to directly encourage pharmaceutical companies to focus on neglected diseases R&D. Because of the potentially small value of the provided incentives in comparison to the market value of profitable therapeutic fields (such as diabetes or cancer), firms are rather unlikely to start researching into neglected diseases while dismissing other core R&D areas. Pull programs may, nevertheless, serve to increase interests and efforts of the private sector to perform the neglected diseases R&D as a niche area within companies' R&D strategies, to stimulate them to

continue with a neglected diseases portfolio, or to do adaptive work for (L)DC needs.

Studies[331], however, indicate that industry involvement occurred without specifically implemented incentivizing mechanisms. Other factors, such as long-term business considerations, Corporate Social Responsibility aspects, or the existence of PDPs are the main drivers for current neglected diseases R&D involvement of firms of each size. Providing extensive economic incentives could change this currently self-motivated approach of commercial entities. In addition, the current debate on incentivizing health tool development for neglected diseases in (L)DCs focuses strongly on the multinational pharmaceutical firms as responsible stakeholder. Instead, other actors, such as universities, SMC and particularly not-for-profit organizations with innovative business models appear to lead the product development for diseases affecting poor countries.

Thus, a promising combination of programs might be push financing through the channels of PDPs and pull incentives to stimulate and support the late stage development process. Evidence suggests the importance of the not-for-profit organizations to encourage various stakeholders to participate in and contribute to the R&D process for neglected diseases, including academia, or the pharmaceutical and biotechnology sector. PDPs are involved in all phases of the pharmaceutical innovation process, ranging from discovery to development, registration and delivery. As organizations dedicated to neglected diseases they manage to focus their collaborators skills and expertise on this area at all development stages, which provides them a particular advantage in comparison to other economic incentives that tend to address only one specific period of the drug innovation. PDPs also appear to provide a more cost-effective way of performing pharmaceutical product development for neglected diseases than the common R&D conducted under the current market-based business model. Moreover, PDPs act as fund allocator and portfolio managers. Contrary to the governments, the not-for-profit or-

[331] LSE Report, 2005.

ganizations have better skills and knowledge to decide on the optimal R&D projects. Thus, using the channel of PDPs to allocate public funding to neglected diseases R&D may facilitate the decision of government agencies on priority projects. Additionally, funding provided to PDPs is for the biggest part reallocated to their partners, including academic and industry collaborators[332]. With first products developed and marketed, the PDP model already demonstrates efficiency. At this still relatively early stage, the R&D performance of the not-for-profit organizations will, nevertheless, require further assessment and monitoring.

The major needs of PDPs are increased financial contributions from various donors, including from public sources, for example, in form of direct funding or other financial mechanisms.

In addition, their R&D performance, particularly for the later development stages of the pharmaceutical innovation process, could be complemented by incentives that stimulate collaboration of other stakeholders with PDPs. These include the summarized push programs, such as tax credits, and pull financing mechanisms of PRV, APC, or prize funds to encourage particularly the multinational companies to provide their needed skills and expertise. Without prejudging the other incentive proposals, it appears that the APC and the PRV schemes are the preferable programs. The APC is designed according to business considerations of pharmaceutical companies, while the PRV can be implemented at low cost for governments but with an interesting benefit for firms. Nevertheless, the prize fund scheme has been introduced at high level for international discussion and consideration with the submission of the proposals form Barbados and Bolivia, in various designs adapted to concerned priority health needs. In addition, the GSPA explicitly refers to the award of prizes for health-related innovation, in order to encourage investments in health products. A high-profile prize may function as stimulant for pharmaceutical companies, but also as intellectual challenge for the scientific community. It will be on governments to decide on their first choice financing models for neglected diseases R&D.

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[332] LSE Report, 2005, pp. 37, 38.

D. Conclusion

This chapter highlights not only the need for innovation of new pharmaceutical products in the field of neglected diseases, but the many challenges in finding the best way to support this R&D. At highest international level industrialized countries and (L)DCs have committed to solve the urgent health problems in resource-poor regions in order to contribute to their socio-economic development and to balance the existing inequality in global health. By directly addressing the health issues prevalent in (L)DCs, the GSPA calls upon governments of Member States and other relevant stakeholders to develop new thinking on innovation of and access to medicines. Neglected diseases are not within the regular business of governments in industrialized countries. In most cases these countries lack the prevalence of these infections, thus often also lack the relevant policies and strategies to spur related innovation of pharmaceutical products. As part of their commitments, industrialized countries have agreed to a more sensitive approach to the health issues in resource-constrained regions. This includes a short- and medium-term commitment to adequately address R&D priorities of (L)DCs in their national health R&D policies. It requires developing and implementing incentive schemes for health-related innovation, thus the integration of neglected diseases in both (national and international) push and pull programs. Push mechanisms, such as tax incentives or grant programs need to be adapted in order to encourage R&D efforts within, but also outside the national geographic borders. The promotion of patent pools and creative licensing strategies for innovation related to neglected diseases must also be stimulated. With respect to pull incentives, the APC, the PRV and the prize fund are further promising programs to supporting innovative science.

The support of organizational models such as the PDPs, however, prompts to be the critical approach for the risk-taking and the stimulation required in the field of neglected diseases.

In addition, the GSPA includes specific actions at other levels to support neglected diseases R&D, including building clinical trial capacities in

(L)DCs and fostering R&D capacity building in (L)DCs as a long-term approach to enable the endemic countries to address their own public health problems.

The various initiatives in the field of neglected diseases of different stakeholders at all levels and from all sectors underscore the desire to contribute to the solution, as well as, an increased awareness of responsibilities towards the needs of poor populations. With the GSPA, the international framework for guiding the efforts is set. The next critical step is its implementation.

PART TWO
Interviews with stakeholders

A. Objectives and methods of the interviews

I. Objectives of the interviews

The foremost objective of the interviews with key groups in neglected diseases product development in Switzerland was to examine their motivation or disincentives to perform or support R&D for neglected diseases, and their perception and overall assessment of the main proposed incentive schemes to stimulate respective R&D. We also tried to understand the needs and difficulties of stakeholders involved in the R&D process. Finally, we wanted to investigate the current Swiss policy engagements in the field of neglected diseases R&D on both the national and international levels and identify areas of possible policy changes or adaptations to further integrate the issue of neglected diseases R&D within the medical R&D environment in Switzerland.

II. Methods

We conducted 23 open-ended interviews with stakeholders from the different interest groups involved in the issue of R&D for neglected diseases including:

- six interviews with officials of various departments and agencies of the Swiss Government;
- five interviews with representatives from the research-based pharmaceutical industry and their national and international associations;
- three interviews with representatives from product development partnerships;
- two interviews with representatives from two Swiss public research institutions;
- four interviews with representatives from non-governmental organizations;
- one interview with an official of an international organization;

- one interview with representatives from the major research funding institution in Switzerland;
- one interview with the technology transfer office of a Swiss university and related university hospitals.

Our goal was to obtain a diversity of views across the various stakeholders that we believe represent a comprehensive and multi-faceted outlook of the underlying issue.

The interviews were conducted during the period of February 2008 to October 2008 as face-to-face interviews or over the telephone, and interview length ranged from one to two hours. The questionnaire had been sent in advance to the stakeholder representative(s). The interviews were recorded and transcribed *verbatim* with the permission of the participant.

The questionnaire for the interviews was divided into two sections: a general part concerning most discussed topics in the field of neglected diseases R&D and a specific part adapted to the interviewed stakeholder and the particularities of his involvement in the subject.

The general part was designed to determine the stakeholder's positions on the issue of R&D for neglected diseases. It was basically guided by four major themes concerning: (1) The definition of the term "neglected diseases" and the assessment of the main problems related to R&D for neglected diseases (for example, scope, cause, etc.); (2) The stakeholder's involvement in R&D for neglected diseases and relevant pharmaceutical products, or his contribution to the R&D process or strategy to support R&D; (3) Evaluation of the performance of PDPs, their contribution to neglected diseases R&D, their effectiveness, etc.; (4) Assessment and support of incentive schemes to stimulate R&D for neglected diseases products. The options for incentive schemes as included in the questionnaire were based on the identification of the most discussed models in literature and studies. The focus was on pull funding mechanisms. We included five proposed incentives, namely the transferable patent extension, prize funds, the advanced purchase commitment, patent buy-outs, and regulatory fast track options, i.e. in particular the Priority Review

Voucher. We also asked participants to assess the proposal of the Medicinal R&D Treaty.

In the second part of the questionnaire we included questions adapted to the interviewed stakeholder according to his group affiliation and particularities of involvement in R&D. The questionnaire for the Swiss Government departments included questions on their assessment of the process of the WHO Intergovernmental Working Group on public health, innovation and intellectual property (IGWG) and Switzerland's role in the process. In addition, we sought to understand how neglected diseases research could be implemented into the Swiss international public health policy, as well as development and national innovation policy agendas. In the case of the private pharmaceutical industry, the questionnaire included an inquiry on the motivation to perform in-house R&D in the field of neglected diseases or disincentives to carry out R&D, respectively. Another question related to the pharmaceutical companies' willingness to collaborate or to provide assistance to other stakeholders that perform neglected diseases R&D activities. The questionnaire for PDPs also included a survey on difficulties these organizations encounter during the R&D process and incentives to encourage collaborations between and with different stakeholders. And finally, with regard to non-governmental organizations (NGOs), we included questions concerning the assessment of the Swiss international public health and development policy relating to neglected diseases R&D.

B. Summary of the interviews

In our analysis of the received data the interviewed actors were divided into three key groups of actors: the group of producers, the group of advocacy, and the group of regulators.

I. Group of producers

The actor group of producers includes organizations that are directly involved in (neglected diseases) research and development of pharmaceu-

tical products, namely for-profit organizations (pharmaceutical companies and their associations), non-profit organizations (PDPs for neglected diseases), an international organization (working within PPPs), and public research institutions.

1. For-profit organizations (pharmaceutical companies and their associations)

a) Definition of "neglected diseases"

The term "neglected diseases" was defined in a broad sense by all interviewed representatives. A common characteristic is the lack of research and adequate treatments for certain diseases because of insufficient markets for these conditions. This includes neglected diseases according to the common understanding, i.e. diseases disproportionately affecting developing countries, but also the rare indications without adequate medical R&D. Focusing on the former, R&D gaps were identified in terms of total absence of treatment; existing treatments with inadequate delivery for developing countries; and mono-therapy diseases, with only one available treatment and a need for alternatives because of resistance.

The "neglect" in the area of diseases affecting poor populations in developing countries was explained by the lack of medical R&D by all industry representatives. The development of pharmaceutical products for these neglected diseases faces the same challenges as the development of drugs for industrialized countries with the specific requirements to make the medicaments "cheap and easy to use in developing countries' environment". Study participants emphasized that the classical business model for pharmaceutical R&D investment applied in industrialized countries is not appropriate for diseases endemic to poor regions, given the high costs and risks in the pharmaceutical R&D on the one side, and the limited financial capacities of the affected populations on the other side. Neglected diseases are not in the focus of the ordinary R&D strategy of a pharmaceutical company, and R&D is not carried out because, in the profitability assessment of the companies, they are not interesting to invest in, as one respondent clearly noted:

> "Focus naturally means to neglect other areas of research. Decisions on areas of focus are based on assessment of the business situation, business perspective according to the classic Friedman approach: where is the company at the moment, where does it want to go, what are the company's strengths, where are the identified best potential business opportunities?"

According to some representatives, "neglect" can also occur under a second aspect: certain diseases cannot be addressed with existing treatments that do not reach patients because of inadequate health infrastructure and delivery systems in endemic countries. With the drugs that are available, diseases and populations are neglected because of political failure of the governments to address their health problems, as one study participant pointed out. This includes the reluctance to create a market for these diseases in the endemic regions. Where developing countries lack capacities to develop incentive programs or lack purchase power, governments should address the international communities and organizations for help.

b) Current policy instruments in Switzerland to stimulate R&D for neglected diseases

Generally, the representatives of the pharmaceutical industry were not aware of policy instruments in Switzerland to encourage R&D for neglected diseases. Some few examples of Swiss involvement in the topic that were mentioned include the Swiss contribution to the Global Alliance for vaccines and Immunization (GAVI) and the PDP Medicines for Malaria Venture (MMV), as well as the support of the Swiss Tropical Institute (STI) and the establishment of the Global Health Institute at the Ecole Polytechnique Fédérale de Lausanne.

c) Main current involvement in R&D for neglected diseases and motivation or disincentives to perform or support R&D

> "We are not saying it is sufficient. We are not claiming that industry cannot contribute more. The industry can and will. There is work on the way."

Pharmaceutical industry representatives emphasized the significant changes in the R&D field over the last ten years and the steady increase of private sector involvement in R&D projects for neglected diseases. At the time of the interviews, the pharmaceutical industry had 50 projects related to malaria, tuberculosis and tropical infectious diseases with the great majority of the research endeavors focusing on the first two diseases. The innovation processes are predominately conducted in partnership with PDPs. In summary, examples of contributions of the pharmaceutical industry vary widely and range from in-house R&D or establishment of research institutions for tropical diseases, to collaborations with PDPs and other pharmaceutical companies and stakeholders. Pharmaceutical industry initiatives also include donations of developed products or drug supply at affordable prices; technology transfer; know-how transfer, for example by training of health care workers in endemic countries or lecture assignments at developing countries' universities; community support and patient advocacy in endemic countries; access to the companies' compound libraries; or the establishment of supply structures for drugs and distribution systems in developing countries.

This increased involvement in neglected diseases R&D was mainly attributed to strong social advocacy by NGOs and public pressure to respond to the public health issues of developing countries; to the increased financial resources available due to high funding by the Bill and Melinda Gates Foundation (BMGF) and others; and to the increased interest of pharmaceutical companies in Corporate Social Responsibility (CSR). A better mutual understanding of the issues surrounding public health needs of poor populations, and a recognition of the important role of the pharmaceutical industry in the process of providing health care

products as essential part of the health delivery system can be felt, as some participants noted.

As a source of general motivation to perform or support R&D for the diseases malaria and tuberculosis, the industry representatives noted reasons such as a strong social advocacy and awareness in these fields; the traveler market; the financial incentives provided particularly by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM); the synergy effects of R&D, such as research results in tuberculosis with a broader ranging use for other infectious diseases; and last, population size providing a higher chance of developing a market for malaria and tuberculosis in endemic regions than for the tropical infectious diseases touching a smaller number of patients.

For neglected diseases without a market in industrialized countries and a smaller number of patients, the general motivation to perform or support related R&D was attributed to two factors: first, the historic involvement of a firm in this field of R&D; secondly, the increased social commitment of pharmaceutical companies that includes projects in the non-profit area.

Historically, companies with a traditional track record in areas relating to infectious diseases or closely related diseases carried this portfolio further. In addition, through mergers companies received new portfolios and continued with some of the projects in-house or by outsourcing the R&D. On the other hand, companies without historical involvement in the field of neglected diseases contribute to this non-profitable sector for reasons of increased CSR commitment. Changes in the ways of doing business within the last years have moved the firms' strategies from a mere business focus to a "triple based approach" that includes socially and environment conscious business orientation as one study participant pointed out. Many companies' business strategies have included CSR and sustainability policies. These approaches have also been influenced by the shareholders' and investors' increased interest in social commitment of commercial entities reflected in the creation of social responsibility and sustainability stock indexes, such as the Dow Jones Sustainability Index or the FTSE4Good index. These financial market measures require

companies to declare social and environmental involvement and engagement. Neglected diseases as such are not reflected in these indexes; this might however change, as companies usually react on the recommendations of index companies. Nevertheless, non-profit areas such as neglected diseases have been embedded into the CSR policies of some firms. Under this doctrine these companies will continue to support the R&D in this field if they can manage to keep their profits in other disease sectors, according to the assessment of another industry representative.

Of the three interviewed multinational pharmaceutical companies, two no longer perform in-house R&D for (tropical) infectious diseases and one is currently directly involved in R&D for some (tropical) infectious diseases. Two of the interviewed pharmaceutical companies had at least one (tropical) infectious diseases product and related R&D portfolio in the past. The reason for abandoning further research was based on two aspects: the lack of an interesting pipeline to continue the R&D or lack of research results for the (tropical) infectious diseases for a long period of time and business considerations. The latter included general changes in the companies' strategies to focus on personalized health care as future direction reflecting the current trend in the pharmaceutical sector, and the concentration on areas where the companies historically had competitive skills and knowledge. The (tropical) infectious diseases field was no longer considered as a priority area, based on permanent future business assessment and competitive intelligence, as one representative emphasized. Further challenges, such as the patent expiry of blockbuster drugs, and innovation issues in the core business areas create high pressure on many multinational pharmaceutical companies today, and reinforce their decisions to concentrate on the commercial fields while setting aside the less profitable diseases, the respondent concluded.

In the aftermath, one of the interviewed companies continued with the manufacture of its product for a tropical infectious disease, intended for the traveler market. The other company supported the establishment of an independent not-for-profit organization, a spin-off from its development department, which now concentrates on the drug discovery process, amongst others for one neglected disease. The company provided

the laboratory infrastructure and a funding grant; in addition, the newly established institute has access to the firm's compound library, as well as the technical and scientific skills. The multinational company has, furthermore, launched an initiative related to the infectious disease that includes the supply of a high quantity of the medical product to WHO, and the transfer of drug manufacturing technology and expertise to pharmaceutical firms in the countries with the highest disease burden. The goal of the initiative was, amongst others, to increase the supply of the medicine and to build up capacities in the endemic regions.

According to the representatives of the two pharmaceutical companies that have left the (tropical) infectious diseases field there are no commercial incentives that could bring their firms back into R&D for neglected diseases. R&D for diseases affecting poor populations is not perceived as a business case but rather as an altruistic endeavor and contributions to this area would be run under this concept or the firms' CSR strategy. One of the two representatives, however, noted that, as a basic principle, neglected diseases could establish a business case in terms of investments in emerging countries such as China, India or Brazil that could pay off in a long term view by creating a global network, building up relationships, trust and, in the end, customers.

Although not in terms of direct involvement, the two representatives expressed the willingness of their companies to contribute to the non-profit and non competitive R&D processes for neglected diseases by other means. This could include, for example, technology transfer, know-how transfer, providing access to the company's compound library or screening activities for potential targets.

The third interviewed company is directly engaged in neglected diseases R&D. Amongst others, it had set up a not-for-profit drug discovery institute for tropical diseases in an endemic country, in form of a PPP. This institute focuses on three infectious diseases (tuberculosis, Dengue fever, malaria). The selection of these diseases was based on the size of the endangered population and the scientific synergy with other R&D fields of the multinational company (MNC). The institute is part of the MNC's research family and has access to all research assets available in the firm.

For the late-stage development phases the institute will look for global partnerships.

The motivational factors for the company's involvement in neglected diseases R&D are manifold according to the representative:

- First, the expectation of business possibilities in a long term perspective. Business in this field is not to be understood in terms of immediate financial returns but in terms of generational investments. Many of the now impoverished regions may constitute emerging markets in 20 or 30 years. Investments and business involvement in these countries create advantages for the future, and, furthermore, help to understand the environment and culture, as the key representative summarized. Neglected diseases can be seen as a business case in addition to hard core business cases in the industrialized countries in terms of sustainability of the pharmaceutical business and growth of markets in a long term perspective.
- Second, the reputational gain. The pharmaceutical industry seems rather badly perceived in society due to the population's lack of understanding of the work of pharmaceutical companies. Involvement in the non-profit and life-saving sector of R&D, and particularly concerning impoverished regions, may help change this perception.
- Thirdly, the scientific synergy effect of the R&D for certain neglected diseases that will have broader ranging use for commercial diseases as well, such as Dengue fever for hepatitis C. Moreover, research results for one of these diseases might be exchanged within the company which may contribute to a faster and more effective R&D process.
- Fourthly, the increased CSR considerations of the company that has shifted the profit-oriented attitude as core mission of the commercial entity to ethical aspects as well.
- Last, a company's engagement in the non-profit sector may constitute a powerful motivating factor in-house. Scientists and other employees of the firm may be motivated by non-profit initiatives and highly inspired to contribute to the lifesaving R&D for diseases dis-

proportionately affecting poor populations. For pharmaceutical industry staff members the non-profit involvement provides some counterbalance to public arguments of animal testing and profit orientation.

The disincentives in the field of neglected diseases R&D that were mentioned by all pharmaceutical industry respondents mainly relate to the drug development process and the lack of health infrastructure in endemic countries. Generally, R&D for neglected diseases faces the same challenges as R&D for any other indication. Specific issues that were pointed out were, in particular:

- the lack of animal models or in vitro models for certain neglected diseases such as Buruli ulcer, leishmaniasis, or sleeping sickness;
- impediments in clinical trial performance in developing countries because of lack of skilled health personnel;
- the fact that, after product development, companies face insufficient supply systems and distribution infrastructure in endemic regions, as well as lack of health workers to provide the medicines. Firms may be challenged to further invest into the development and establishment of drug delivery systems in developing countries, as one representative noted;
- cultural divergence. One respondent illustrated this aspect by the following example: free drug donations for a tropical disease provided to a developing country by a pharmaceutical company were accepted only after two years of intensive negotiations with the government. Reason for the delay of delivery to the endemic region was the distrust of the country's authorities as to the donation of the pharmaceuticals. The multinational pharmaceutical company was suspected to provide low quality or poisoning products.

d) Evaluation of incentive mechanisms

> "Pharma industry has to be part of the solution because of the drug discovery and development part. If you want them you need to operate in an environment which would not scare them away."

Overall, pharmaceutical companies want to be involved in R&D for neglected diseases. There is a high degree of awareness of the R&D issues surrounding diseases affecting disproportionately poor populations, a willingness to perform or contribute to R&D and to consider new incentive models as encouragement. Unanimously, however, the respondents emphasized the importance of IP and particularly patents, as irreplaceable for securing continuation of and investments in pharmaceutical R&D. Any new incentive model that jeopardizes the classical business model is not acceptable, as one participant pointed out. The trade-off provided by the patent system is regarded as a very solidary and sharing system: IP protection gives companies the incentive to invest in and perform R&D and recoup their investment during a limited exclusivity period, in return for the disclosure of knowledge to the society. Before IP protection, the only way to protect investments was secrecy. Patents have solved the risk of and secrecy of innovation, as one key representative summarized. Public discussions on IP, however, focuses on issues of disclosure, access to medicines, compulsory licensing and others. However, any society that was successful in making economic use of innovation had patents. IP rights are necessary for innovation, and abuses should be addressed by changes and adjustments of the system of IP one participant noted:

> "Abolishing the patent system would eliminate the pharmaceutical industry and pharmaceutical R&D – an entire part of society capable to make new medicines."

The orphan drug regulations are the best proof to show that exclusivity rules work to stimulate pharmaceutical R&D according to another industry representative. Both rare indications and neglected diseases face the issues of lack of market and lack of research. The market exclusivity rule of orphan drug regulations provides an even stronger protection than patents, because the exclusivity can only be broken by products for the same indication with a significant improvement.

The industry representatives, however, admitted that the IP system is not efficient in stimulating R&D for neglected diseases. Incentivizing the area of neglected diseases without industrialized countries' market and small patient size was seen as difficult. A new mechanism, to be attractive, would need to create a win-win situation for companies by providing both financial and reputational gains, according to some study participants. Strong emphasis was laid on defining potential incentive schemes as addition, and not as alternative, to the existing IP based model.

Overall, all **incentive proposals** presented were not perceived as sufficient to stimulate a multinational company without a neglected diseases portfolio to start R&D in this field. The models do not offer the same strong incentive effect as the current market-based business system protected by IP and do not encourage multinational companies to switch core business areas to the much less profitable neglected diseases R&D field. However, some mechanisms could encourage companies that have a neglected diseases portfolio to continue the R&D in addition to their core business cases. It could also motivate R&D activities of companies that may be able to create synergies between their core research areas and the neglected diseases, or the adaptation of existing drugs for other diseases, such as the neglected indications. Certain incentive mechanisms could also promote collaborations with PDPs.

With regard to the presented pull incentive mechanisms, most support was expressed for the Advanced Purchase Commitment (APC) and the Priority Review Voucher (PRV). The **APC mechanism** was seen as in line with the companies' business considerations. It simulates a market situation; moreover it is modeled as a binding contract which constitutes

normal means of doing business for firms. Overall, however, it was identified as an agenda for companies with already existing neglected diseases portfolios or cases for product adaptation for other diseases, but not as effective to stimulate original R&D. The major drawback recognized was the upfront investment a company would have to provide for the neglected disease R&D at risk to fail. In consideration of the high failure rate during the product development process, it appears to be too risky for smaller biotechnology companies to perform the research. For multinational entities, however, the APC sum provided might be too small to stimulate investments. The "second mover" issue as a question of designing an effective APC was also raised as concern. The APC would have to be created in a way that the second manufacturer with the better product has to win also, because using the weaker product would not be justified, as one respondent noted.

The **PRV** was also perceived as favorable. As incentive, however, it encourages incremental innovation or follow-up R&D of companies with neglected disease portfolio or related in-house R&D rather than initiating R&D, according to all respondents. Issues of practicability and ethics were recognized as disadvantage: increased numbers of PRV could delay life-saving breakthrough drugs if human resources of regulatory agencies remain limited. Some participants further emphasized that the implementation of the PRV incentive in Switzerland alone would not be enough because of a small market size. In this case a regional approach in collaboration with the European Union would be more suitable.

The **transferable patent extension** was refused as incentive mechanism. Although acknowledged as an attractive model by the companies' representatives because of the potential financial and reputational gains, it was described as too theoretical and as politically not feasible, due to belated generic product entry and national health budget restraints. The industry associations rejected the mechanism for the same reasons and included as further disadvantage the resulting market distortions for important drugs in areas such as cancer and others in the case of patent extensions for related drugs.

Patent buy-outs, as the other IP related incentive model, were assessed as a very weak and theoretical mechanism. The inherent problem of the incentive is the economic validation of the patent by the sponsors and governments as buyers. Instead, company representatives suggested sharing licenses over patents that are not within the firm's core business, but of interest for another party to perform neglected diseases R&D.

Prize funds were perceived as less favorable by most industry representatives. Main drawbacks acknowledged were the requirement of advanced investments, as already mentioned for the APC proposal, that makes the model less suitable for SMCs due to high uncertainty, and the sum provided through the prize fund not attractive for multinational companies to shift research priorities form a profitable sector to a neglected disease supported by a prize fund. The prize would have to be an equivalent to the "bold figure of the current pharmaceutical market" to be a real alternative, as one respondent noted. Design issues on the criteria for providing the prize and the "second mover" issue were addressed as further setbacks. One representative, however, perceived the prize fund as a "good idea" if it is designed as a voluntary system that intends to complement the patent system, and concluded that the proposal could be attractive for players in the emerging markets to add to their portfolios the prize related project as an interesting addition.

The **Medicinal R&D Treaty (MRDT)** was opposed by all industry representatives as a mandatory system that would inhibit R&D performance and inventiveness as currently generated by the market model. Recognized conceptual shortcomings of the proposal were the centralized system of decision that would cause too much bureaucracy, unnecessary loss of financial resources for the administration, and the complexity to adapt the suggested credit system.

Further incentives proposed and supported by the industry representatives include both push and pull mechanisms. The stimulation or **funding of basic and transitional R&D** on neglected diseases in Switzerland performed by universities and research institutions, such as the Swiss Tropical Institute or the Global Health Institute of the Ecole Polytechnique Fédérale de Lausanne, was seen as very important. Furthermore,

two key representatives suggested **tax credits** for pharmaceutical companies that perform research in the field of neglected diseases, for example for activities such as the collaboration with universities and other research institutions. The goal and advantage of tax credits would not be to particularly increase the already good cooperation between private and public sector in Switzerland in the field of medical R&D, but to attract more foreign commercial research investments into the country, as one participant emphasized. Further possible tax relevant actions could include clinical trial performance or screening activities. To attract more and different stakeholders the group of beneficiaries could be extended to other contributors or donors, such as banks, that support neglected diseases R&D.

Funding of PDPs was viewed as an immediate and essential way of supporting neglected diseases R&D.

Further possible encouragement schemes proposed by industry respondents include the financial support of **purchase agreements such as the Global Alliance for Vaccines and Immunization (GAVI)** and other similar approaches that also focus on the distribution of the developed products in endemic countries. As another pull program, the **"Fund for R&D in Neglected Diseases"** was suggested by one representative. This novel funding body financed by governments and other donors would focus on diseases without market incentive, in order for commercial entities to invest in R&D. The proposal is based on the assumption that the current early stage pipeline for neglected diseases products needs significant funding to continue the development process. Funding would be allocated based on a modified process of portfolio management as used in the pharmaceutical industry according to technical, medical and scientific criteria, however, without the potential return assessment. Projects at any stage of research and development originating from universities, research institutions, PDPs, or pharmaceutical or biotechnology companies would be funded from one decision point to the next. New obtained data could be presented to the fund as the basis for the decision of whether to continue to the next R&D stage. IP would stay with the innovator; however, in return to the allocated funding the fund would re-

ceive an exclusive license for the neglected diseases indication. Advantages associated with the R&D fund were that no advanced investments are required; its attractiveness also for the biotechnology industry; possibility of evaluating projects against appropriate target production files and competing projects; finally, the integration of the fund program into the current medical R&D model and neglected diseases R&D environment.

Policy options outside the incentive discussion were also mentioned by industry representatives. One key respondent emphasized the high impact of good education in public health and suggested **grants for training programs** for scientists and health workers in endemic countries. Know-how transfer could be provided on different aspects ranging from basic and transitional research, to the drug discovery process, clinical trials or regulatory procedures.

Another industry representative referred to the necessity of an **international overall concept on neglected diseases** "as tool kit for the different stakeholders" under the auspice of the WHO. This plan would provide guidance to all actors and include shared responsibility of all stakeholders. Nationally, Switzerland could provide a **policy framework** prepared by the different governmental departments to bring all stakeholders at all levels together "in a modest and sustainable way", as the respondent further suggested. A third participant viewed the **reorientation of the Swiss development assistance** to the issues related to public health in developing countries and neglected diseases as necessary.

Ideally, a variety of different incentives should be provided to interested actors, enabling them to evaluate the incentive benefits based on their own business model, capabilities and scientific considerations in relation to the required R&D investments.

Both push and pull incentives should be included. Despite their advantages and setbacks, incentive schemes such as the APC, the PRV on European level, and the prize fund were viewed as "something that needs to be tried out". The integration of various incentives into an international or a national legal framework, such as the orphan drug regula-

tions, was not viewed as favorable. A Swiss approach in implementing such legislation, although a powerful sign for other countries and stakeholders would have marginal impact due to the small market in the country. A regional approach in Europe or legislation in the US was viewed as more effective. One representative of the pharmaceutical industry associations noted that he has never been asked by member companies to initiate legislative changes, showing the lack of interest for a legal framework for neglected diseases similar to the orphan drug regulations.

e) Product development partnerships

> "Personally, I think it is the only way of encouraging and stimulating neglected diseases R&D."

Overall, industry respondents emphasized the high impact of PDPs on the increased R&D efforts for neglected diseases. PDPs were perceived by all representatives as very successful and important in stimulating neglected diseases R&D and generating a product pipeline for neglected diseases where there is no dual market opportunity. The PDP model provides a shift from a pure business-oriented model of a pharmaceutical company to a health-oriented one, as one industry representative noted. PDPs work without the business pressure of the classic business model in meeting certain bench marks such as sales and profitability thresholds. Moving into a public-private partnership reduces and takes away business pressure for pharmaceutical companies, making the collaboration with PDPs attractive, as he concluded.

All three representatives of pharmaceutical companies previously worked or continue to work within public-private partnerships. Their contributions to the endeavors range from the provision of laboratory infrastructure, in-house skills, to the development and financing of integrated programs, grants for the creation of research institutions and ac-

cess to compound libraries of the company. These partnership experiences also include collaboration with and support of PDPs focusing on neglected diseases without markets in industrialized countries. In these cases the companies mainly provided access to compound libraries, technical or scientific in-house skills, tools for R&D performance, or possibilities to use the company's laboratory. As principal motivation for collaboration with PDPs and goals of the companies, representatives mentioned reputation gains, creation of relationships in other markets and the establishment of markets.

The funding provided by PDPs was viewed as the main advantage of partnering with the organizations. It enables pharmaceutical companies to continue financing late stage development of products for which they do not have prioritized funding within their R&D budgets and therefore would not be developed otherwise. PDPs, further, distribute the risks associated with pharmaceutical R&D to multiple partners. Their concept creates a virtual community of interest between industry and the public sector academia in a specific field of diseases. It links and combines the different skills of the various partners. One participant emphasized the experiences of PDPs in neglected diseases endemic countries as very favorable. A successful product development not only requires an understanding of the molecular biology of diseases but requires, in addition, an understanding of the culture, the physiognomy of patients and the environment of the targeted region, as he summarized. PDPs employ staff members with field experience, such as DNDi with staff members from Médecins Sans Frontières. Finally, collaborating with PDPs provides a learning effect for the pharmaceutical company.

A major drawback acknowledged was the lack of sustainable funding of PDPs that may inhibit collaborations and the continuation of development projects. Many of the PDP R&D projects are still in the lower-cost early stage of the development process. The expensive clinical trial phase is still ahead and finances are lacking.

Direct financial support of PDPs by governments and other donors was viewed as a very important factor to sustain and increase R&D performance in the field of neglected diseases. Furthermore, the creation of in-

centives that support collaborations of industry and other stakeholders with PDPs was emphasized. This could include tax credits on research or the establishment of a prize fund or an APC for a certain category of diseases. One further example mentioned was the establishment and public funding of public-private collaborations in the field of neglected diseases according to existing models, such as the Innovative Medicine Initiative, a joint technology program of the European Community and the pharmaceutical industry aimed at supporting the faster discovery and development of better medicines for patients for certain diseases prevalent in Europe.

Generally, pharmaceutical companies are prepared to continue and to expand collaborations with PDPs in the future and to provide support to their not-for-profit R&D for neglected diseases, as emphasized by all representatives.

2. Not-for-profit organizations (product development partnerships for medicinal products and diagnostics for neglected diseases)

The PDPs participating to the study are entities that have been specifically set up to develop pharmaceutical health tools for diseases disproportionately affecting developing countries. They have been established within the last ten years.

a) Definition of "neglected diseases"

Most PDP representatives define "neglected diseases" in a more narrow sense when compared to the description provided by the pharmaceutical industry respondents. The definition includes diseases that are mainly prevalent in developing countries, connected by a lack of research and the common characteristic that they do not represent a market for pharmaceutical companies because of the financial limitations of the affected population.

Orphan indications were not considered as "neglected diseases" because of the market opportunities provided in industrialized countries in par-

ticular by health insurances for even the minor rare disorders. "Neglect" is related to the poverty of affected populations. As one representative noted:

> "The difference is that these diseases in a very disproportionately manner affect poor people. There is a very clear relationship between the diseases and the poverty factor and poverty is one of the main reasons for these diseases to exist."

The classification of the diseases in TYPE I, II, and III diseases as provided in the report of the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) and adopted by the WHO was acknowledged as useful.

The "neglect" of certain diseases prevalent in developing countries was attributed to the lack of pharmaceutical markets in the endemic regions, resulting in disinclination of the pharmaceutical sector to invest. A further element of neglect mentioned by PDP respondents is the lack of interest of governments from both industrialized and developing countries to address the health issues. This includes administrative interventions to substitute the investment deficit of the private sector: generally, market failures are addressed by government programs and incentives to stimulate investments, as was the case for the orphan diseases. In the case of neglected diseases, governments, however, have not contributed to adopt measures to encourage R&D. This also includes developing countries, according to the PDP respondents. As one participant noted:

> "We should not bi-polarize the world. Developing countries such as India and Brazil have the capacities on the one side and the problem on the other side. For these countries it is a real choice to create incentives to attract some investments in neglected diseases. They have also "neglected populations" who live far outside the big cities."

b) Motivation for R&D in neglected diseases and advantages of product development partnerships

The core mission of PDPs is to develop, manufacture and deliver affordable high quality health products for low resource settings in endemic countries. The PDP foundation partners recognized the lack of health tools and interest of the private pharmaceutical sector to invest in R&D for diseases different than the illnesses in industrialized countries, and established the non-profit organizations to tackle the R&D gaps.

The form of a virtual company without laboratory and own R&D performance was developed out of necessity. It could be launched quickly with small staff requirements and reasonable start-up funding, as one study participant mentioned.

PDPs see their vision to address critical urgent health issues in developing countries and their not-for-profit approach as particular advantages. Contrary to the for-profit entities, PDPs can carry out R&D for health tools that address public health needs according to best industry practice without the need to consider aspects of market dynamics, cost recovery, profitability assessments or shareholder expectations that drive private sector R&D. This freedom is provided by private and public funding that PDPs receive for performing the product development. Without these financial resources from donors, it would not be possible to develop health products according to their mission and to their underlying business model.

Additionally, the form of a virtual non-profit entity has created an incentive effect for pharmaceutical companies to perform or to contribute to R&D for neglected diseases. Collaborating with PDPs allows industry partner to share the risk of product development in the neglected diseases area with multiple partners, and to lower the costs and risk of investments.

All respondents considered PDPs as the **most cost effective way** of carrying out R&D for neglected diseases. The pharmaceutical industry business model was viewed as inappropriate for R&D activities in this field because of inherently high development expenditures. The PDP

model is based on externalizing and outsourcing and allows R&D performance in the cheapest possible way, as one representative pointed out. This was attributed to three reasons. First, PDPs can select cheaper collaborators. Second, (industry) partners of PDPs are often asked to contribute to the development costs. PDPs see themselves in a good position to negotiate a good rate for R&D performance of their collaborating parties. With industry collaborators they often conclude agreements of a 50 percent contribution to development expenditures; smaller companies, however, receive the full costs. Finally, PDPs conduct a large part of R&D activities in endemic countries where the expenses for R&D are much lower.

The **combination of private sector and public sector skills and knowledge** provided by PDPs was mentioned as a further advantage: PDPs employ professionals with pharmaceutical industry experiences and public health specialists, particularly from developing countries. This allows non-profit organizations to collaborate with partners from both sectors, as well as international organizations. They act as brokers between the private and public participants to make the needed health technology available in endemic regions. Additionally, multinational companies (MNCs) acknowledge the access to the other PDP partners, particularly from developing countries, as an advantage and reason for collaboration, as one representative emphasized.

The PDP model also allows **employing creative intellectual property (IP) policies** to leverage the organizations' objectives of affordability and access to health products in developing countries, according to the study participants. The contractual language of PDPs concerning intellectual property rights (IPRs) includes strategies that are in support of their mission, for example on pricing of the innovation, product manufacturing, market segmentation or technology transfer to PDPs or developing countries. Although they also manage their IP portfolio to protect the IP produced by the partnership, the PDPs' IP approach differs from that of for-profit companies. They have no need to protect their market position and profits by excluding competitors from access to their markets; they are open to sharing knowledge and projects with other organizations that

are developing health technologies for the same market. As one representative noted:

> "Another cornerstone is a clear IP policy and how to manage that. Who do we want to protect by the IP policy. IP policy is about who you want to protect. Companies want to protect their shareholders. We want to protect our shareholders. Our shareholder, our target population is the public health sector in developing countries. Our IP policy is based on that concept of knowing where these people are, who can serve them best and then protect that particular population with accessible and affordable price for what they need."

The collaboration with various partners from the private and the public sector worldwide additionally provides the opportunity for **knowledge sharing and technology transfer to developing countries**. Major parts of the neglected diseases R&D happens in endemic regions. Developing country collaborators can benefit from the collaboration with partners from industrialized countries that, among others, contribute their skills and knowledge in the pharmaceutical R&D process. Moreover, carrying out clinical trials in the endemic regions the host population provides the benefits of training and educating the local population. For the majority of the interviewed PDPs, knowledge and technology transfer along with technology impact assessments and capacity building in developing countries is part of their organization's policy.

c) Current conditions for R&D in neglected diseases

In general, the current conditions of performing R&D for neglected diseases were described as better than one decade ago. This was attributed to the increased awareness and interest in (L)DC public health issues, which resulted in increased funding in this area.

The solid background of basic research in the field of neglected diseases was emphasized as an advantage for the drug development. Contrary to medicinal product development, basic research in this area was never abandoned, particularly because it provides some learning effect for other fields. For example, the genome sequence of many parasites has been mapped, providing important knowledge for discovery and development processes. Moreover, because of the abandonment of R&D for a long time, the chance of success in neglected diseases drug development was assessed as being higher than the chance of success for the new product development with high investments within the last decades.

For the field of diagnostics, however, the basic research was perceived as insufficient.

Within the product development for neglected diseases essential gaps and obstacles exist at any stage. This includes, for example, steps such as the identification of genomic leads; or difficulties during the clinical trial performance in developing countries. The former is usually performed by the biotechnology and pharmaceutical companies. Screening activities, however, have been abandoned by the private sector because of economic reasons. In the case of **clinical trials**, limited capacities in developing countries impede the research. This includes the lack of trained and qualified personnel in endemic countries, as well as strong regulatory agencies that can perform the related activities in an appropriate way, for example, the assessment of the risk-benefit for the patients in terms of efficacy and safety. Furthermore, patients live in very challenging settings which increases the difficulties in performing clinical trials.

IP was outlined as a further possible barrier to R&D performance of PDPs. All PDP representatives acknowledged that, in general, they could license needed technologies. However, they emphasized the difficulties and time consuming processes in receiving the right to use the inventions in many cases. One respondent outlined this by an example:

> "It took us for example one year to do a patent review a certain technology which is the simple technology people use for these pregnancy tests. The IP around that so simple technology which you would think that it is generic that everybody can use is an incredible nightmare. The assessment on the IP and how many patents have been develop for this is almost 800 pages long. And then you need to understand how your technology, your idea infringes some of the patents; that is very complex and requires good knowledge of people who have done that for a living. […]. That part is a huge obstacle that can be overcome, but still exists."

Most difficulties in licensing important technologies arise in negotiation with (United States) universities and small biotechnology companies, according to the representatives. For the latter entities, IP is the most valuable asset for receiving venture capital, as one respondent emphasized. Universities in Europe, on the other hand, were considered as much more open in their licensing practice.

The **continuous lack of sustainable funding** was highlighted as major drawback by the PDP representatives. A not-for-profit organization starts a R&D process without the security to end it due to the uncertainty in finding the financial resources. The lack of finances impedes negotiations with partners and has significantly slowed down the process of many projects, as one respondent admitted. It further causes ethical issues in some cases. The financial uncertainty often endangers the completion of clinical trials; trial participants, however, agreed to their involvement in the expectation to continue until the end.

The PDP representatives expressed their disappointment about the public sector commitment and funding. As one respondent noted:

> "R&D of not-for-profit organizations happens for the public sector for public goods. But the public sector has never decided that this is important enough to ensure that there is finance."

Although awareness of the neglected diseases issue and the work of PDPs have increased, as well as financial contributions to related R&D, there is still a lack in systematic funding mechanisms for health technology innovation. Governments commit considerable contributions to purchasing foundations such as the Global Fund for HIV/AIDS, tuberculosis and malaria that focus on already approved pharmaceutical products. Donating to purchase institutions, however, also requires supporting R&D organizations that are supposed to develop the products that will be taken up by the funds to be distributed, as one respondent criticized. He further mentioned a lack of mechanisms from governments to deal with entities such as PDPs. Public sector funding of health R&D for developing countries often falls into the responsibility of two or more departments, for example the science and technology, health agency or the development agency. The former department regularly finances early stage research, while the latter focuses on access to medicines and work within the developing country. The not-for-profit organizations often do not correspond to the remits of neither of the departments, as the representative noted. Another obstacle mentioned was the short term of public funding commitments. Traditionally, public sector financing is provided on an annual basis, which constitutes difficulties for PDPs that have commitments for a much longer period during the product development process. Lobbying the issue before governments, however, has resulted in a financial commitment from three to five years in some cases, which is more efficient from the forecast and financial flow point of view, as one respondent pointed out.

d) Current conditions for PDPs in Switzerland

One participant emphasized the advantages of being situated in Switzerland. Foremost, the country provides very good scientific conditions at the basis. This includes, for example, academic research as well as the highly evolved biotechnology sector or the strong pharmaceutical industry in the country. In addition, Switzerland hosts the international or-

ganizations. He viewed these factors as very important for the work of PDPs and as a very good environment to establish important contacts and create synergies with other organizations. Nevertheless, the representative regretted the fact that the Swiss government does not establish ways to capture and coordinate all this intelligence and know-how in a way that is supportive of PDPs and other activities in R&D for new health tools for neglected diseases in Switzerland. He further expressed his disappointment that the Swiss government does not institute any kind of formal relationship with PDPs. This runs contrary to other countries that uphold a continuous dialogue with PDPs that is not necessarily related to financial support, but to a general interest in the work of PDPs and their performance. This lack of political interest in Switzerland raises also questions in other countries and sometimes inhibits fundraising outside Switzerland, as the study participant noted.

e) Policies and incentives to support product development partnerships' R&D performance

Overall, PDPs emphasized the need and importance of increased **governmental engagement** to address public health issues in developing countries and to create a policy environment and funding that can stimulate and accelerate health technology innovation for neglected diseases in industrialized countries. Within a comprehensive approach to improve the effectiveness of pharmaceutical R&D for poor populations, PDPs view their role as crucial, particularly because they already develop new technologies for use by developing countries and provide product pipelines. Moreover, they have been successful in joining scarce resources and creating partnerships between various stakeholders from the private and public sector. While providing the most cost effective way of product development, PDPs also support others in continuing their research. Multinational companies that carry out neglected diseases discovery are likely to search for public money as soon as they enter the clinical trials phase. In this case, they often turn to PDPs to finance the more expensive development part, as one representative noted.

PDP respondents viewed **sustainable funding**, including increased public sector funding, as key factor and indispensable not only for the support of R&D processes of PDPs, but also for R&D for neglected diseases in general. Steady financial flows are a question of sustainability of the organizations and of confidence in the engagement with other stakeholders, as well as for the employees of the PDPs. It facilitates the R&D performance of PDPs and demonstrates financial reliance for interested stakeholders, particularly potential industrial partners. Funding could be provided in traditional forms such as *grants* or from non traditional sources. In this respect, one respondent suggested the initiation of an *International Finance Facility for neglected diseases* as creative financial model. Governments would underwrite commitments to be placed via bonds into the capital markets to raise cash flow over years. The representative viewed this initiative as an innovative and effective way of raising money for neglected diseases R&D from both public and private sources. The establishment of a *global R&D fund* was also proposed as instrument to generate funding on the multilateral level.

One respondent considered it as important to adapt or **change the structural organizations of government departments** in a way that combines both research and development within one division or to define one responsible department in order to deal with the neglected diseases issues, including R&D of health technologies. Structural changes also include **extending the duration of financing agreements between PDPs and the public sector to offer a more sustainable funding basis.**

Facilitating access to knowledge at an early stage to enter into the R&D process was also mentioned as another essential factor to assisting the R&D performance of PDPs. This includes the creation of a supportive IP environment. Knowledge generated by academia or publicly financed institutions should be accessible. For this, it was suggested that the European countries and Switzerland should include a principle obliging academic or publicly financed groups to make knowledge available to PDPs and other not-for-profit entities performing R&D for developing countries. One respondent viewed a WHA global strategy and plan of action (GSPA) that comprises this principle and requires member states

to translate it into national legislation as a global solution for access to important knowledge related to developing countries' R&D.

Sustaining basic research in the area of tropical infections was another essential aspect highlighted by the PDPs representatives to meet future needs for product development in the field of neglected diseases.

Further policy proposals of PDP representatives were related to the **regulatory process** to facilitate the neglected disease drug approval process. One respondent suggested providing the Swiss regulatory agency Swissmedic with a mandate to employ part of their financial and human resources to perform the regulatory process for neglected diseases, and to provide scientific opinion to neglected diseases products. This proposal actually refers to the implementation of a rule in Switzerland equivalent to Article 58 of the European Regulation No. 726/2004[333] that establishes a mechanism whereby the European Medicines Agency may give a scientific opinion in the context of cooperation with the WHO. The provision addresses the need to protect the public health and to give scientific assistance to non-EU-member countries, while also enabling rapid access to those countries for important new health tools. Contrary to the European system, that was considered as very complicated and time consuming, the Swissmedic system would be much easier and faster to use. The creation of support of North-South collaborations for technology and knowledge transfer with regard to regulatory activity was also addressed as a factor supporting approval procedures in developing countries and by that the R&D process for neglected diseases.

Two PDP representatives outlined the **Value added tax (VAT) payments and taxes** as an obstacle that could be overcome and would provide a possible area of support of PDPs by the Swiss Federal Government and cantonal Government. According to the estimation of one of the respon-

[333] Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (consolidated version; 6/7/2009). Available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf, accessed on 18 September 2009.

dents, this could make the difference of up to one million dollar a year for his organization that could be saved and resorted to R&D projects instead. He suggested a change of the legal status of the PDPs as Swiss foundation to the status of an international organization. This provides certain advantages, for example in terms of tax obligations of the PDP or its employees. It would also exempt donors of PDPs to pay Swiss income tax and VAT.

Last, the PDP representatives suggested the **creation of a (network) structure for neglected diseases R&D within Switzerland** that links all competitive advantages of the country, such as the strong medical research environment, academia, the biotechnology and pharmaceutical industry, the international organizations, PDPs, and others, as way to facilitate their work. All PDPs situated in the country could be of value and the Swiss Government should find ways to exploit this as an advantage. This bridge could be very easily built with relatively small amounts of money but with a lot of visibility for the Government and tangible result for the PDPs, as one respondent noted.

f) Evaluation of incentive mechanisms

Overall, PDP representatives expressed no support for giving pharmaceutical companies direct incentives to stimulate R&D for neglected diseases, for example patent extensions and others. The main reason was the cost inefficiency of this approach. To stimulate pharmaceutical companies to start R&D in the non-profitable area of neglected diseases, the value of an incentive mechanism would have to replicate the current very high value of the pharmaceutical market. In comparison, the multisectoral partnership approach was assessed as much more cost effective. The incentive proposals are, furthermore, inappropriate to address the fundamental issues in discovery of drugs, vaccines, or diagnostics that the pharmaceutical industry is facing today, namely the need to lower the initial risk of the heavy upfront investments. Thus, initiating one of the incentive schemes will not encourage pharmaceutical companies to start neglected diseases product development. Instead, firms are rather

likely to contribute to the R&D processes of PDPs or other organizations under a no-loss-no-profit approach. This has also been confirmed by a survey[334] on the motivation of companies to perform or support neglected diseases R&D, as one respondent pointed out.

The PPDs respondents viewed securing sustainable funding of the current R&D projects for neglected diseases as the best short term intervention and an essential policy challenge. In their opinion, the proposals to stimulate multinational companies (MNCs) would not meet the reality of the present situation that R&D for neglected diseases, in fact, is already performed by the PDPs. Any incentive that would be established, would subsidize R&D results that will be reached many years later due to the long product development process. PDPs, however, provide the product pipelines at the present moment which requires immediate support. On the short term basis, securing sustainable funding of the current PDP R&D projects for neglected diseases was viewed as the foremost policy challenge.

Study participants viewed improvement of reputation, the existence of financially reliable partners such as PDPs, and positioning in a potential future market as the current motivation of multinational and small- and medium-sized companies to participate in health technology innovation for developing countries. PDPs as financially reliable partners were described as the best way to influence the firms' R&D strategies to contribute to the unprofitable R&D sector of neglected diseases. At present, this offers enough advantages for the private sector to contribute to neglected diseases R&D, always provided that they do not lose money, the PDP representatives assumed. The few pharmaceutical companies with neglected diseases portfolios perform R&D without further incentives. This has also been documented by various studies[335], as one respondent emphasized. Moreover, securing distribution of the developed products under a functioning public health system in endemic countries would

[334] LSE Report, 2005.

[335] For example the LSE Report, 2005.

provide more important incentives to these firms than some of the proposed financial mechanism.

One respondent viewed the discussion on the different incentive proposals as an avoidance of the real problem: the leadership of governments to tackle the issue of diseases affecting poor regions and populations. This requires commitment of countries, in particular to provide the financial resources that are needed.

This includes that countries and country groups such as the G8 fulfill their promises related to funding of solution of public health problems in developing countries. Moreover, donor countries can use their influence and convening power to get more governments involved.

In the assessment of the PDP respondents, some of the incentive models could be additional programs to the current business model of the pharmaceutical industry and the multi-sectoral partnership approach to encourage R&D for neglected diseases.

One representative emphasized the importance to link any encouragement scheme to delivery. For example, for a drug that has been developed with a PDP and passes phase I of the clinical trials, the company would receive a priority review voucher; if the drug passes phase II and III, the developer would receive a PRV; in addition, if the product has been developed within a period of five years, the firm would be awarded with a patent extension for a certain time.

APC and PRV received the most attention from the PDP representatives because of their recent pilot implementations. In accordance with the pharmaceutical industry's evaluation, they viewed the APC scheme as a possible incentive to stimulate R&D involvement at the end of the development process but not as suitable to encourage pharmaceutical companies to enter into the neglected diseases R&D. The low value of an **APC** in comparison to the pharmaceutical market, the need of upfront investments and the insecurity in the strength of the donors' commitment over the long product development time were mentioned as main disadvantages of the scheme. The pilot initiative for pneumococcal disease was described as a "one-to-one deal" for a product that has already been

in development before the launch of the program, and for this reason does not fall under the criteria of an APC as it has been developed.

The **PRV** faces the same drawback of rather supporting ongoing R&D without the potential of initiating original R&D performance of pharmaceutical companies. One respondent additionally noted the ethical issues surrounding the use of the regulatory process as incentive vehicle and the possible obstacles of impeding the accelerated approval of life-saving products. However, if the governments consider potential implementation of the incentive scheme, it should be at the European level.

The **patent extension** was evaluated as a possible incentive of significant importance for pharmaceutical firms, particularly because of the imminent patent expiry of certain blockbuster drugs. However, the implementation was seen as not feasible for the political reason not to inhibit or delay generic product entry. **Patent buy-outs** were viewed as too theoretical. One respondent added that the scheme assumes IP as a problem, as a barrier for access to the developed products. In the case of the diseases affecting only developing countries without a global market, however, this is not an issue. Differential pricing, parallel imports and other related topics are not a problem in the field of these neglected diseases.

Similar to the APC scheme, **prize funds** were criticized for not being in line with the business model of the pharmaceutical industry. Companies would have to provide high up-front payment in the perspective of the guarantee of a certain amount of money after product development. Due to high uncertainty, this model is not perceived as stimulating MNCs' or small and medium-sized company's R&D for neglected diseases.

The Medicinal **R&D Treaty** was also opposed and one respondent referred to the, at the time of the interviews, ongoing IGWG process as a more suitable solution on the international level.

As **further possible incentives**, PDP representatives mentioned particularly innovative finance programs as of main interest. Possible schemes that were suggested to provide needed funding were the establishment of a *global fund for neglected diseases R&D* as already recommended by the WHO Commission on Macroeconomics and Health; furthermore, the ini-

tiation of an *International Finance Facility for neglected diseases*[336]. Programs that reduce the R&D costs were further proposed. This includes, for example, a regulatory process *fast track options for neglected diseases* products and the *waiver of registration fees* before the registration authority.

Technology transfer was mentioned as possible policy for capacity development in poor regions. This includes, for example, the establishment or support of *training programs for regulatory agencies* in developing countries to increase their capacities, as a possible field of North-South collaboration. Moreover, it was suggested that governments should find ways to *facilitate and encourage technology transfer by all stakeholders*. New incentive and financing mechanisms to stimulate R&D for neglected diseases, could include provisions that most of the related R&D and production activity should be transferred to developing countries in order to increase R&D and production capacities in these regions.

The implementation of incentives within a national legislative framework such as the orphan drug regulations was not seen as suitable. Solutions for the public health issues in developing regions and neglected diseases R&D require an international approach. One respondent emphasized the need to set up an international framework and strongly supported the development of the GSPA. The IGWG process was viewed as a very important forum for discussions and critical for the implementation of a framework that could stimulate R&D. The developed GSPA structure would provide flexibilities that enable the national adaptation according to each country's environment and preconditions. Another respondent, however, evaluated the, at the time of the interviews, ongoing IGWG negotiations as inefficient. The results of the process would not provide progress to what had been already discussed and recommended, but repeat what has already been evaluated for several years. In the end, it is the role of the governments to execute the developed and proposed recommendations in these surveys. This commitment, however, is still lacking to date for the most part, as the representative concluded.

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[336] See paragraph (4).

3. Public Research Institutions

The actor group of public research institutions (PRI) includes a recently established university institute for basic research on cellular and molecular microbiology for infectious diseases and a university associated institute with focus on research and services, including, for example, screening activities and regulatory clinical trials for drugs and vaccine development, in the field of tropical infections.

a) Research involvement and motivation to perform R&D

The recently launched PRI concentrates on studies in basic biological mechanisms underpinning infectious disease research, as well as in translational research like drug discovery and vaccine development in the fields of tuberculosis, leprosy or HIV/AIDS and other retro-viral diseases. The institutions' mandate, moreover, includes teaching activities. Although not directly involved in neglected diseases research, the studies may create scientific synergy effects for the research in diseases such as tuberculosis, Buruli ulcer and leprosy, according to the institute's representative. Funding is provided by the Swiss Federal Government, and the research groups also receive finances from the Bill and Melinda Gates Foundation (BMGF), the European Community the US National Health Institute or the Swiss National Science Foundation (SNF). The institute was established because of the importance of the health problems and the scientific interest, while increased funding resources in the fields have not played a specific role, as the respondent noted. Science was the driving factor and the interest in understanding specific problems to take the research to the next stage.

> "Funding is extremely important but it should not be the decisive factor in his context. Scientists have to have certain independence. The curiosity driven stuff is still very important."

The institute is collaborating with national organizations and partners in Switzerland, as well as laboratories in Europe, the United States and developing countries. However, it intends to extend partnerships. The collaboration with pharmaceutical firms that have a long-term commitment in the area of the institute's research focus is particularly interesting, as its representative pointed out.

> "Lots of the major public health problems are things that cannot be solved within one or two years. You would ideally like an engagement for ten years. Because that is the length of the cycle from discovery research to the use in the clinics."

The other participating institute is a well-established research organization with the mandate of research, services and teaching in the field of international health. It focuses on tropical infections, for example malaria, tuberculosis and sleeping sickness. The institute's activities include basic research, development of new intervention tools, epidemiology, control of infectious diseases, as well as health care interventions, health service management and clinical and diagnostic services. It employs an interdisciplinary approach. The operational focus is in Africa, Asia, Eastern Europe and Switzerland. The funding channels are the competitive mechanisms of the SNF, in addition to philanthropic sources such as the BMGF and others. In addition, the institute receives revenues for the services provided in the field of public health and for clinical research for drug and vaccine development. It maintains intense collaborations with other stakeholders in Switzerland and internationally, particularly with developing countries. The motivational factor of the institute is its commitment to work on neglected diseases and to contribute to worldwide health development, as the study participant representing the research organization noted.

b) Definition of "neglected diseases"

The PRI representatives viewed as neglected those diseases that are not in the interest of R&D entities, including particularly the private pharmaceutical sector. They basically mentioned the tropical infections, such as leishmaniasis, Buruli Ulcer and others. Orphan indications were not perceived as neglected diseases under the generic definition. Moreover, malaria and tuberculosis were not included because of the high attention and funding the diseases receive.

According to the respondents, R&D on neglected diseases has been abandoned because of lack of profitable markets and incentives for the private pharmaceutical sector to perform the product development. One study participant, however, pointed to the enormous changes that happened within the last ten years in the field of neglected diseases. Significantly increased funding and the substantial number of groups and companies that are presently working in the field of neglected diseases field, make these epidemics not neglected anymore, according to his opinion.

c) Current conditions for R&D performance

Generally, the PRI representatives expressed high appreciation for the R&D environment in Switzerland. Moreover, the Swiss education and science policy was described as excellent and supportive. The establishment of one of the PRI, for example, was funded by the Swiss Federal Government.

The increased financing resources in the area of neglected diseases facilitate R&D in this field, as one respondent pointed out. He referred to the expansion of R&D at his organization and the related human resources growth. This R&D emergence was attributed to strong leadership at the institute as well as to the augmented funding, particularly by the philanthropic foundations. The collaboration with other actors was perceived as very good, professional, with mutual input and understanding. This includes contractual relationships in a top-down situation with PDPs or pharmaceutical companies, as well as cooperation on the academic level

with university groups in Switzerland or worldwide. The representative further mentioned the extensive exchange in the field of trypanosomatids (for example, sleeping sickness and leishmaniasis) on the academic level in Switzerland, including an annual informal meeting between the involved researchers that work on the organisms.

Difficulties that were portrayed by the respondent include cultural differences between the various collaborating partners. The representative further noted experiences of inhibiting effect of IP policies when working within consortia.

> "In consortia we have lived through situations that IP was a huge obstacle between universities and companies. We have actually a funding gap in a grant with the Gates Foundation. They wanted this to be sorted out before they pay. And we almost had to cancel a development program. It is a huge obstacle. And here are many difficult questions to be solved over all."

Performing clinical trials in developing countries was also mentioned as problematic. The respondent described the general problems on the basis of sleeping sickness as example:

> "Sleeping sickness: it has the same problems. It is a rural disease, with high impact but low prevalence. To run a clinical trial we have to screen thousands and thousands of people to have a few in a clinical trial. And then you are still working in the middle of nowhere. So we have to establish research centers, train people who come from nowhere in terms of education. There is no electricity, no trained people, no logistics. In addition, the issue is to find the balance of how much you have to invest, how much training to get to a decent result and not violating the rules. Thinking about the informed consent when people have never heard the word "research". We try our best.

> And we translate everything in local languages, have witnesses, and have extensive processes in informing populations and individuals."

To improve the clinical trial process in resource-poor countries, the study participant proposed to build up a broad basis of medical personnel, university educated and trained in research topics, and located in the capitals of the developing countries as a long-term goal.

d) Current policy instruments in Switzerland to stimulate R&D for neglected diseases

According to one respondent, Switzerland does not take an active role in the support of R&D for neglected diseases, be it in the administrative sector of the Swiss Development Cooperation, or in the services of education and research provided by the State Secretariat for Education and Research and the Swiss National Science Foundation (SNF), the latter as the country's main funding body for basic research. The rather passive approach of Switzerland was attributed to the lack of political commitment in the field of neglected diseases that results from the inexistence of these epidemics in the country. Swiss initiatives and interests in neglected infections are based on personal commitments of individuals rather than on a sustainable and structured governmental approach, as the study participant noted. Apart from the common statement on the Swiss Health Foreign Policy that embodies the objectives of Switzerland's foreign policy in the domain of health, the respondent was not aware of further governmental instruments in Switzerland with global health as concern. Cooperation between the relevant departments of the Swiss administration, however, was assessed as very complicated with a lack of coordination between the different agencies. Instead, a joint venture between the State Secretariat for Economic Affairs and the Swiss Development Cooperation for foreign projects was perceived as more efficient. As Swiss initiatives potentially related to neglected diseases R&D the respondent mentioned the Swiss participation to the European and

Developing Countries Clinical Trial Partnership, that aims at accelerating the development of health tools for prevention and treatment against HIV/AIDS, malaria and tuberculosis, with a focus on phase II and III clinical trials in sub-Saharan Africa; and the initiation of a funding call by the SNF in the year 2006 on research partnerships with developing countries that aim to promote North-South scientific relationships to strengthen the scientific competence and achievement of research in developing regions. With a view on future political involvement in Switzerland, the study participant wished more active State partners at all levels, including the administrative sectors of the State Secretariat for Education and Research, the Swiss Development Cooperation or the SNF. With respect to the latter, he acknowledged the good funding policies of the organization, however, proposed that funding calls such as the one on research partnerships with developing countries in the year 2006 should become "a routine".

The other study participant viewed Switzerland's excellent education, and its science policy and medical research environment as a factor that could be used for the benefit of neglected diseases R&D. Recognizing the advancements in technology as very important for the country's economy, Switzerland has wisely invested in science, technology and higher education which resulted in a high standing in the "scientific league table", the respondent noted. He perceived an increased political commitment of the Swiss Government as a decisive aspect to make use of this strong scientific environment for the field of neglected diseases. The development of natural synergies that exist between the various stakeholders situated in the country is one way of possible interventions, which the study participant assessed as easy to be established due to an agreeable mind-set of most of the actors. A further proposal was to launch a "flagship" program for a certain disease that the Swiss Government considers as important in terms of its relations with certain countries, for example, and a related long term (financial) commitment that goes beyond the normal governmental cycle.

e) Evaluation of incentive mechanisms

In general, the representatives were not familiar with the incentive proposals. They emphasized, however, the need to have industrial partners for the development of products because of the competitive skills of the pharmaceutical industry in fields such as the regulatory process and others.

Public pressure was perceived as a decisive factor for the current involvement of the pharmaceutical companies in R&D for neglected diseases. Pharmaceutical companies, but also their shareholders, should be remembered of their social responsibility and the importance of their active participation in the development of health tools for the prevention and treatment of diseases not prevalent in industrialized countries, as one respondent noted. Nevertheless, the representatives agreed on the importance of finding mechanisms that offset the development costs for the pharmaceutical companies, in order to get them involved in the field of neglected diseases. The private sector responds to market forces and incentives should address this business approach. One respondent supported the **PRV** as being in line with corporate thinking and as a potential mechanism to stimulate pharmaceutical industry R&D involvement. **PDPs** were also seen as a suitable way of stimulating neglected diseases R&D. Collaborations within partnerships allows the industry to perform R&D under a no-loss approach and to receive reputational gain in addition. Therefore, incentives should be designed to encourage industry actors to enter into partnerships.

4. International Organization

The international organization participating to the study provides a global program that funds R&D on infectious diseases of poor populations, and supports capacity building in disease endemic countries.

a) Definition of "neglected diseases"

In a broad definition of "neglected diseases", the representative included any indication for which there is insufficient market to justify commer-

cial R&D for health products in industrialized countries, as well as developing countries. He concluded that most of these indications are infectious diseases, however, that this approach could also be applied to other areas of ill-health. The issues within the field of neglected diseases occur because the existing economic mechanisms and processes do not allow the delivering of health tools to those who need them, he added.

b) Current conditions for R&D performance and shortcomings

In the respondent's eyes, the environment for product R&D for neglected diseases is better than it has ever been. Philanthropic and public sector financial resources encouraged private sector involvement, which significantly increased, including in-kind contributions to PDP/PPP. Besides, the public sector has recognized the importance of the private sector and appreciates the value of efforts of the pharmaceutical industry to the health sector. The increased activities and number of stakeholders engaged, however, has made the R&D environment more complex and created new issues and challenges, as the respondent emphasized.

As one main drawback, the respondent identified a remaining lack of "joint-up thinking" in the field of neglected diseases R&D. The newly involved organizations and institutions had to learn to operate and work together in this area within the last years. Nevertheless, there is still a substantial deficit in mutual understanding and mistrust between the public health sector and the private sector and their according functions. The public sector, for example, needs to be skilled further in the commercial innovation process and the related risk taking, as the representative emphasized. He illustrated this view by the example of the significant investments a pharmaceutical company had to undertake to provide the largest scale of production of any drug ever for non-profit.

Furthermore, there is a need to raise awareness of fields that are still under- resourced. According to the respondent, the challenge for the near future is to identify the fields of diseases that receive overly funding and to redirect some of the finances to areas that are underserved.

The current IP system was not viewed as a particular hindrance that needed to be overcome. In the view of the respondent it is a question of negotiation and of developing an agreement that allows the industry partners to use the innovation for the profitable markets. Most of the agreements that had been concluded by his Organization had other issues than IP. The representative viewed the current role of his Organization in working within the current system, changes in the area of IP having to be left to the political forces.

c) Incentives to support R&D for neglected diseases

Due to the ongoing IGWG process at the time of the interview, the representative did not give an extensive assessment of the presented incentive schemes. In very general terms he suggested to implement forms of encouragement such as tax credits and other mechanisms that offset a company's costs or opportunity costs in order to motivate the private sector to engage in the neglected diseases R&D process, and particularly to participate in PDPs or PPPs. In addition, he pointed to the importance of increased engagement of governments. This includes the promotion of the issue of neglected diseases among stakeholders in their countries and the need to partner, for example within PPPs or with PDPs, but also the promotion and directing of international organization to the issue; furthermore, the allocation of funding to R&D initiatives; and last, a clear commitment of governments to the international organizations and their importance in directing the international collaboration and policy setting that is also supported by augmented financial resources to the international bodies such as the UN, the WHO, and its special programs for infectious diseases of poor populations. The latter aspect was emphasized as particularly eminent because of the increasing responsibilities and operational activities of the international organizations. As an example, the respondent noted the rise in the number of agencies his Organization has to interact with, from three or four institutions ten years ago to 40 at the present time, with an increasing tendency. The international sector needs to be scaled up competitively to be able to cope with the overload of engagements, as he concluded. Financial contributions, however, should be

provided to facilitate the work of the international bodies and not to control them.

Beyond the generation of new health tools for developing countries, the respondent emphasized the importance of the promotion of capacity building in the resource-poor regions in order for them to be able to address their own health issues.

With regard to Switzerland, the representative highlighted the specific role of the country because of the international organizations it hosts and its strong pharmaceutical industry. This position provides an opportunity to act as a mediator and to link the public and the private sector, as well as other stakeholders.

II. Group of advocacy

The actor group of advocacy includes non-governmental organizations (NGOs) that are involved in the questions of public health, innovation and intellectual property, or are leading campaigns on public health issues of developing countries and the issues of pharmaceutical R&D in neglected diseases.

1. Definition of "neglected diseases"

All interviewed NGOs define "neglected diseases" according to two factors, namely the lack of medical innovation for certain diseases for a long time and the lack of interest of the pharmaceutical industry to perform R&D because of deficient purchase power of the affected populations. They typically concern the tropical infections in developing countries. Most NGOs also include diseases with profitable markets in industrialized countries (such as HIV/AIDS, diabetes type II, malaria, or tuberculosis) where existing products are not well adapted to developing regions' use. However, two participants broadened the scope of diseases to areas with pharmaceutical gaps in general. According to these representatives the "neglect" is linked to the failure of the pharmaceutical innovation to respond to medical needs in developing countries on the one

hand, and to "neglected" pharmaceutical innovation areas in industrialized countries such as antibiotics or some rare diseases without R&D, on the other hand. Another representative suggested the definition as provided in the United States tropical disease PRV regulation that includes a statutory list of diseases and other not listed epidemics primarily affecting poor people living in developing countries or vulnerable populations. Despite these different approaches and scopes of "neglected diseases", all representatives agreed for reasons of simplification to the use of the classification of Type I, II, and III diseases (with Type II diseases as the neglected areas of R&D and Type III diseases as the most neglected areas of R&D) as provided in the CIPIH report and adopted by the WHO IGWG.

The "neglect" in medical innovation occurs because of market failure. The affected countries do not provide a profitable market for the pharmaceutical industry to invest in R&D for neglected diseases prevailing in these regions. As a common point of view, most interviewed NGOs emphasized two reasons for the lack of pharmaceutical R&D for certain diseases: first, the malfunction of the pharmaceutical market model and its underlying IP-based innovation system as a whole; and second, the lack of public leadership to tackle the issue of neglected diseases. The current IP-based and demand driven pharmaceutical R&D is oriented towards profitable markets. It links the development of medicines to the financial capacity of the targeted population and results in market-driven rather that health needs driven R&D, leaving unprofitable but important innovation areas underserved in both developing and industrialized countries. In addition, the IP-based system causes access problems to essential medicines, in particular, but not exclusively, in developing countries. This requires an integral discussion on the issue of R&D of health tools and access to these products after development.

2. Evaluation of incentive mechanisms

Based on this opinion, all interviewed NGOs agreed that the current IP-based model for stimulating pharmaceutical R&D is not working for ne-

glected diseases (as referred to Type II and III diseases) and that there is a need for new incentive models. One representative noted:

> "…We want something where the product is affordable and there is no exclusivity at the end."

The issues in the field of neglected diseases are of public interest and do not present a market interest situation. According to all health activists, this requires a strong involvement of the government in the whole neglected diseases issue. Governments should give the direction and monitor the whole process from basic research up to delivery of developed products. This also includes government control and establishment of public accountability processes for the contributions of the Bill and Melinda Gates Foundation (BMGF) as principal private funder of R&D for neglected diseases, in order to provide public leadership in terms of R&D and investment priorities.

One representative emphasized that pharmaceutical companies are commercial entities and they cannot be expected to start R&D in a non-profitable field. Their interest and value in performing or participating in neglected diseases R&D includes aspects such as philanthropy, reputational gains, knowledge accumulation and its application in other more profitable areas of R&D, or the learning effects through collaboration, rather than the commercial interest. The perspective, therefore, should be on determining where industry can be useful, how pharmaceutical companies can contribute to the R&D for neglected diseases, and under which conditions. The focus in terms of incentives should be on push mechanisms and the support of basic research. Governments' involvement in the product development process should concentrate on incentive mechanisms for the pharmaceutical industry that allow for better control options in terms of R&D focus, access to the developed product, quality and quantity and other related factors.

Good incentive mechanisms should achieve three goals: innovation, access and technology transfer. In consideration of the scarce resources, a

large number of research projects to be funded and unmet health needs in developing countries, one informant emphasized the importance of focusing on the economic efficiency and efficacy of the incentive system. Thus, the best models for him are those that break the vicious cycle between costs of R&D and end price of the product to ensure affordable access to the innovation. According to most NGOs interviewed, the preferable incentive is therefore the **prize fund** scheme, as alternative or addition to the patent system. The main reasons are the incentive effect that includes both a financial reward for product development based on the health impact and a reward in terms of recognition for the developer, whilst separating the development cost from the price of the end product; the possibility of focusing innovation on certain areas of need; the possibility of designing the model without exclusivity rights, allowing for immediate access to innovation and facilitated technology transfer; and the option of government involvement in and control of the development process. However, concerns were also raised about an intelligent design of prize fund to serve the needs of producers and funders or the estimation of an attractive and appropriate amount as prize.

The **APC** was viewed as less favorable to stimulate R&D for neglected diseases because of unsolved issues concerning access to innovation and technology transfer. Further disadvantages mentioned by the NGO representatives were consistent with those highlighted by the respondents of the pharmaceutical industry and the PDPs, concerning the inappropriateness of the APC to encourage early stage R&D and the question of intelligent design of the contract between donors and potential developers. One participant criticized a recently established pilot APC for several reasons:

> "…(a) It explicitly says that it is actually not set up to stimulate R&D. (b) It is set up for a vaccine that has a global market. It has a big market in the rich countries. Why do you have to set up an APC? (c) The way it has been set up means that of the 1.5 billion more than 600 million will translate in share profit, as we calculated. It could be set up differently and you can save a lot

of money. (d) You end up in a price negotiation, discussion of price justification."

The mechanism of **patent buy-outs** was seen as a method to ensure access to innovation, but not as solution to encourage product development for neglected diseases.

No support was expressed by the representatives of civil society for the schemes of the **transferable patent extension** and the PRV. The former model proposal was considered as a "very expensive way of doing things". The patent extension for a blockbuster drug could translate into hundred millions of profit, which, however, implies a higher financial burden for health insurances or consumers in industrialized countries. One representative also pointed out that the reward in the form of transferable patent extension is not connected to some quality control of the developed product for neglected diseases or efficiency requirement. The **PRV** was objected for the same reasons of lack of efficiency and lack of quality requirements for the developed neglected diseases products. Fast tracking has to be based on medical needs, and the decisions to be made for public benefit on a risk-benefit decision. The whole regulatory process should not be a tradable good and needs to stay independent, as emphasized by one participant. The expanded use of the mechanism could, moreover, slow down the process for priority medicines in industrialized countries.

The **Medicinal R&D Treaty (MRDT)** was seen by most NGO representatives as the way forward for the future in a globalized world. Issues of worldwide concern are easier to be solved at the international level than by national mechanisms. The framework of an international treaty provides the platform for both governments from developing and industrialized countries to contribute to R&D and decision-making in this area. It further focuses R&D on global priority areas. One representative particularly endorsed the freedoms provided in the treaty proposal. Governments can choose the way of supporting R&D, for example in the form of direct funding, the IP system or other incentive models such as the prize

fund. The respondent further emphasized the shift of perspective from IP related issues to the amount of financial contribution that would come with a global R&D framework as important advantage of the R&D treaty proposal. For a third participant the idea of a MRDT was, although one of the "boldest" proposals, still very theoretical, and would need further development.

Further possible incentive mechanisms suggested and supported by the NGOs are **patent pools** for innovation related to neglected diseases. One representative mentioned the option to establish a **global fund for R&D** for health issues affecting developing countries.

All participants agreed to the importance of having both push and pull incentives to encourage R&D for diseases of the poor regions. Push funding and grants are seen as indispensable. These contributions could be completed by the pull mechanism of prize funds, as mentioned by most participants. One representative suggested using the five proposals of Barbados/Bolivia[337] as models for designing funding solutions adjusted to the prevailing health issues. Another participant noted that the ideal combination of the incentives would have to be designed around the particular health problem. For a specific area of diseases, different incentive combinations might be needed, e.g. for drugs and diagnostics. Diagnostics have more basic science issues and require therefore higher push funding contributions as part of the "incentive mix".

3. Product development partnerships

PDPs are perceived as a suitable way to stimulate R&D for neglected diseases in consideration of the tremendous changes in this field that have come with the advent of these organizations. For one representative, PDPs provide an important lesson in terms of pharmaceutical R&D. Their performance proves that product development is also possible in different settings outside the industry model. The cost figures provided by the PDPs present important facts for policy makers to realize that it is

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[337] *See* Part One, chapter C. II.2.b) (2), and footnote 275.

possible to tackle the issue of neglected diseases and to fund this area outside the current market business model. In consistence with the opinion of the pharmaceutical industry respondents, the NGO representative emphasized the importance of increased efforts to improve the sustainability of PDPs, which means particularly higher and perpetual funding. However, all NGO respondents agreed, like other study participants, that PDPs, although a critical part of the solution in the neglected diseases issue, do not provide a long term solution. Such a solution requires foremost the commitment of developing countries to tackle their health problems; the sensitivity and solidarity of industrialized countries in using their R&D capacities; increased financial volume and development cooperation. Accordingly, the engagement of more actors in neglected diseases R&D needs to be encouraged through appropriate incentives. The small number of PDPs for neglected diseases can handle only a limited R&D portfolio, while a much higher investment in and a stronger commitment to this field are required.

4. Switzerland's role

Most NGO representatives are not aware of a distinct policy by Switzerland for public health issues concerning developing countries. The country's role, however, is considered as absolutely critical in addressing the issue of neglected diseases.

> "…We want commitment."

Political and financial commitment of the Swiss Government to the public health problems concerning disproportionately poor populations on both national and international levels was seen as indispensable, particularly in order to provide important signals to other stakeholders, such as the pharmaceutical industry, donors and WHO member States. Nationally, it was suggested that forms of support by the Government should include, for example, the financing of R&D; promotion of the

topic of neglected diseases among stakeholders in Switzerland; the implementation of the GSPA in Switzerland; and making use of the strong medical R&D environment of the country to foster neglected diseases R&D. According to one representative, Switzerland provides certain advantages, such as a good scientific community, financial capacities, pharmaceutical industry capacity, important competitive knowledge within the industry, and, furthermore, a traditional non-political cooperation with other countries. Linking and exploiting all these facilities, the country could valuably contribute to the solution of pharmaceutical R&D for neglected diseases. The representative emphasized, however, Switzerland's strong protective position concerning its commercial interests and industrial policy that would be rather difficult to change. Instead, he assumed a stronger role of the country through the channels of development cooperation, the country's scientific community and the use and sharing of the knowledge within the pharmaceutical industry. Developing medical products for diseases affecting poor populations is been seen as part of a broader approach concerning health issues of developing countries. As a long term solution, one participant asked to integrate public health issues of developing countries into the Swiss development cooperation policy. This would include particularly two steps: first, to raise the **Swiss Official Development Assistance** up to the internationally committed target of 0.7 percent of the gross national product, in order to provide the increased financial resources that are needed; second, to build up an institutional structure within Government departments ("naturally within the Swiss Development Cooperation Agency") responsible for public health issues of developing countries. This could be a person or a body within the administration that initiates, coordinates, and monitors related Swiss contributions on national and international levels.

On the **international scene**, Switzerland was seen as a key country, particularly in the, at the time of the interview, ongoing IGWG discussions. One representative acknowledged the country as having been supportive in many ways in the CIPIH based on the fact that Ruth Dreifuss chaired the Commission. According to his assessment, Switzerland has

made very significant contributions to the problem analysis. The country's position in the ongoing international discussions on solution models and the efforts in implementing the GSPA that will be undertaken by the country will influence other stakeholders. As he notes:

> "…If they say that they are in favor of some of these approaches and that they should be further examined that would make a huge difference. And if they would set up some mechanisms initially on a smaller scale that would also send an important signal or would allow to further see how it works in practice. It is not only about the absolute money that one individual country can contribute but it is also important to move the process forward."

III. Group of regulators

This group of actors is not directly involved in R&D of pharmaceutical products. Nevertheless, it includes actors affected by or taking policy decisions relating to neglected diseases and research and development in that field, such as public health, intellectual property, development cooperation, research and science policies, or IP and licensing strategies. The group includes particularly Swiss governmental agencies and departments.

1. Definition of "neglected diseases"

Neglected diseases were defined in various ways by the representatives of the actor group of regulators, which also displayed the scope and nature of their involvement in the subject.

One respondent declared the neglected diseases as those illnesses that do not exceedingly contribute to the global burden of disease scale, but may have tremendous health impairments for specific populations. In summary, he included any disease that is a burden for a specific population and for which there is a lack of health products. The definition is based

on the disease system and can be de-linked from geographical boundaries.

Another study participant referred to the designation provided by the WHO, based on some common criteria that neglected diseases have in common, such as affecting the poor populations; occurring mainly in tropical climate zones; mostly parasitic and infectious; with a lack of medicinal products; and the difficulties of physical availability due to deficient logistics and distribution systems in endemic regions.

The respondents involved in the multilateral negotiations on public health, innovation and IP referred to the Type I, II, and III classification as an appropriate approach for a definition, with Type II and III diseases as neglected and most neglected diseases respectively. One representative noted the difficulties during the IGWG process to determine the scope of the definition, including in particular the questions whether to concentrate only on the Type II and III diseases, on general developing countries needs in the Type I, II, and III diseases, or on specific developing countries' needs in Type I, II and III diseases. Focusing on the needs of developing countries requires including Type I diseases that also have a relevant patient number in industrialized countries. Giving an example, the study participant mentioned diabetes as Type I illness and Insulin as required treatment. Heat stable Insulin is not necessary in industrialized countries, but in others, often developing regions, it is a basic requirement. The respondent pointed out that depending on the scope and context of the definition of neglected diseases, the underlying issues and questions to solve will vary in terms of access to products and all IP related problems such as compulsory licensing, parallel import or differential pricing; political agendas on public health, research or economy, and other aspects.

Other respondents, not directly involved in the neglected diseases and underlying issues, perceived the term "neglected" as relating to diseases with large medical needs and lack of private sector pharmaceutical R&D.

Most respondents, however, agreed to the WHO's Type I, II, III disease classification as appropriate "working term", with the last two group ca-

tegorizations being termed as the "neglected" and "most neglected" diseases.

In accordance with the other interviewed stakeholders, the officials viewed the lack of market incentives as the principal reason for the neglect in R&D of health products for resource-poor countries. For one respondent, this presents an issue of research ethics. Interesting and promising compounds are abandoned by the private sector R&D because of economic reasons instead of considering their contribution to the public good.

Another official emphasized that the issues in the field of neglected diseases do not concentrate on the lack of health tools and related R&D but occur throughout the whole innovation cycle. He referred to the CIPIH report[338] and its findings of lacks in basic and applied research, as well as in the development of products and their distribution to those who need them.

2. Current policy instruments in Switzerland to stimulate R&D for neglected diseases

As a general comment, the representatives of the Swiss Government felt that Switzerland has no direct incentive to integrate the neglected diseases R&D issue into the Swiss political agenda. One official noted:

> "Switzerland has no natural incentive to do something in this area. The topic has never really been a subject coming from the political side. It has never been a subject from the parliament. There is no incentive to do anything. There has not been anything to force government or parliament to launch full grown initiatives."

[338] CIPIH Report, 2006.

Thus, the national initiatives and policy instruments to encourage or support R&D for neglected diseases vary widely and provide a rather "piecemeal approach". Prominent examples of national initiatives include particularly the early involvement in special programs and financial contributions, for example to the PDP Medicine for Malaria Venture, the Global Forum of Health Research, the Special Programme for Research and Training in Tropical Diseases (TDR) and the Special Programme of Research Development and Research Training in Human Reproduction (HRP), as well as the support of the local environment in developing countries to perform R&D and to build up capacities within the regions. Further program examples concentrating on the area of research are the Swiss participation in the 7th Research Framework Programme of the EU; the involvement in the European and Developing Countries Clinical Trial Partnership (EDCTP); the establishment of the Global Health institute in Lausanne, and the setting up of a Global Health Program at the Graduate Institute of International and Development Studies in Geneva, that includes a policy part and negotiation within the field of global health.

At the policy level, the foremost example mentioned was the founding of the interdepartmental expert group that includes Government agencies such as the Federal Office for Public Health (FOPH), the Swiss Federal Institute of Intellectual Property (IIP), the State Secretariat for Education and Research (SER), the Swiss Agency for Development Cooperation (SDC), Swissmedic (the Swiss regulatory agency for drug approval), or the Ministry of Foreign Affairs. The responsibility for this group is shared between the FOPH and the IIP. Each participating sector analyzed the recommendations of the CIPIH report with regard to its specific domain, effect of the proposals on the agency's policy and framework, and possible areas of assistance to implement the recommended actions. At present, many of the proposed actions of the CIPIH report are already realized, as one official noted. The second important goal of the cross-departmental groups was to build coherency in the Swiss policy. The problem of neglected diseases is complex and involves different government departments. The interdepartmental expert group creates a

platform where the various offices can learn from each other, influence each other, and furthermore build trust to work towards political coherence. The group aims at finding a coherent position of Switzerland on the subject of neglected diseases in international forums such as the WHO or the World Intellectual Property Organization. One result of the cross-departmental group was the common statement on the Swiss Health Foreign Policy. As strength of this statement, one respondent emphasized the underlying assumption that recognizes a continuum between domestic health policy with sectors such as global health epidemics, appropriate health care, and development questions. Another respondent, however, expressed his disappointment that the agreement does not consider action points or policies on health product development, for example, for neglected diseases. Switzerland should have a commitment in the topic, as well as related policies and correlative financial support, he concluded.

The lack of increased finances for global health was pointed out as major drawback of the policy statement on global health. Other countries double and triple investments in this field, as one key official mentioned. In Switzerland the budget has not been provided, although the Government had passed a motion to augment financial support. In this respect, the respondent noted:

> "Switzerland is very good, prominent and progressive in policy coherency and in the negotiation process at the international level, but not so good at financing."

A third official further illuminated the budget issue with special view on the development sector. According to his assessment, health is not given a sufficient priority within the development cooperation. This results particularly in lack of funding for international health. Currently, the Swiss contribution to international health concentrates on work in governance, the empowerment of civil societies in developing countries, the promotion of gender equality, and humanitarian aid. Although these

strategic priorities in health are important to improve the overall health environment in developing and emerging regions, investments in the health sector remain limited. The neglect of health as priority area of the Swiss development cooperation contributed to the lack of increased Official Development Assistance (ODA) budgets. Politically, Switzerland has never committed to the 0.7 percent GDP target for ODA, as the representative noted. The Agency spends less than ten percent of its overall ODA on health related areas, which was viewed as too small in terms of actual needs and international quantitative objectives related to health, such as declared in the Millennium Development Goals, but also in comparison to other development cooperation departments, such as the United Kingdom's DFDI with a contribution to health of above 20 percent of its total ODA. In the absence of an increase in Swiss ODA the stronger reorientation of the SDC responsibilities towards health, as well as resource distribution remains a future aspiration. To be able to act according to the actual scope of issues in the global health sector there is a need for much higher investments from the Swiss Government to contribute to new international programs and to engage in innovative initiatives that are less usual business, the official concluded.

According to another respondent, the Swiss initiatives or programs related to neglected diseases have been developed because of personal commitments of individuals. He saw a lack of political commitment in Switzerland to follow an agenda on diseases of resource-poor countries in a structured manner. He viewed the current debates within the Government as a subject of the spirit of time, as a fashionable topic that started in the 1990ies, but with the tendency to lose interest. He emphasized that more people with a background in public health are needed on government level. In order to initiate changes within the Swiss Government, lobbying the topic of neglected diseases would be required. This can be done by knowledgeable persons within the administration, by creating external pressure by talking to parliament members and Swiss stakeholders, or by an international push toward that domain.

Last, one representative described the difficulties of defining a policy in the field of neglected diseases as a result of its complexity. He illustrated

this with the example of promoting basic research directed to areas of needs. Basic research is bottom up driven. Thus, it becomes difficult to redirect basic research when the best policy approach is not to interfere with R&D programs at all. Drivers of basic research are curiosity and other aspects, such as reputation. The challenge is to create awareness in a way that the curiosity driven researcher knows about neglected diseases and start performing the R&D out of curiosity.

3. Department's or institution's strategies to support R&D for neglected diseases

a) Public Health: Swiss Federal Office of Public Health (FOPH)

The FOPH's competence includes matters related to health policies at the national and international levels. According to the interviewed representative, both areas are closely related and influence each other. In consideration of the issue of neglected diseases he referred to some existing links between Switzerland and developing countries in terms of public health issues. One is the problem of national policies on differential pricing and parallel import of pharmaceuticals. Another link is the incidence of diseases of developing countries in Switzerland due to travels or immigration of affected persons. Relying on this relation to solve the innovation issue in the field of neglected diseases, however, will not be sufficient, the representative emphasized. For some neglected diseases the link may automatically create an incentive mechanism for the pharmaceutical industry to develop products, for example for malaria. In the case of an anti-malaria medicine, one producing pharmaceutical company may provide the same product under different brands: for the traveler market more expensive, and for the developing country market at marginal costs. This incentive mechanism of the traveler market, however, does not function for neglected diseases such as leishmaniasis.

The Agency is well aware of the problem of neglected diseases, however, does not employ specific strategies to support the R&D of health products for these epidemics. According to the representative this field is not within the remits of the Department for Public Health. Nevertheless, the

Agency often acts as a broker between stakeholders to proceed in the process related to the neglected diseases and their underlying issue.

b) Development Cooperation: Swiss Agency for Development and Cooperation (SDC)

The main guiding principles of SDC's involvement in health are the promotion of sustainable approaches adjusted to the capacities of the partners and recipients; equity; the promotion of gender equality; and empowerment. The Agency's strategy in prioritizing health includes the strengthening of health systems' good governance, the development of health systems adapted to the economic situation of the population with special focus on vulnerable groups; or the control of major communicable diseases, particularly HIV/AIDS, tuberculosis and malaria, with prevention at heart. Its operational contributions are concentrated, among others, on fostering health cooperation between stakeholders at the national, regional and international levels; on policy making and decision taking in order to promote research investments according to the needs in health research; on institutional and individual capacity building; on activities concerning other parameters of poverty, such as education, nutrition, income generation and economic development; and humanitarian aid in health.

Following this approach to health, the SDC generally sees its part not in the support or performance of R&D for neglected diseases but rather in assisting the conduct of R&D by the local environment in endemic countries, as well as to contribute to the establishment of R&D capacity in those regions. As a key example, one representative mentioned fostering projects or supporting initiatives in developing countries that aim to set up appropriate institutional review boards and ethical boards for the assessment of research trials. In the opinion of the representative, the role of governments is to ensure that the framework conditions are good enough in the supported (L)DCs so that progress can be made, but not to finance drug development. Accordingly, the SDC is engaged with different stakeholders on a policy dialog level, aiming also to ensure that the

principles of the Swiss development cooperation, such as empowerment of populations or gender equity, are integrated into programs.

Nevertheless, SDC also provides financing contributions to international programs related to research on neglected diseases. This includes, as already mentioned[339], funding to the Global Forum for Health Research (GFHR) or the TDR, as well as the PDP Medicine for Malaria Venture.

Within the Swiss Health Foreign Policy framework, the SDC has the lead for the medium-term goal on research for development. However, this goal does not include health product development but the promotion of research to strengthen the empirical basis for effective health interventions, and the option to influence the dialogue on global research priorities in health in order to reduce the burden of diseases in developing regions in a sustainable way.

The SDC, together with the SNF, is further involved in running the Swiss participation to the European and Developing Countries Clinical Trial Partnerships (EDCTP).

These examples of the involvements of the SDC in global health and more specifically in the field of neglected diseases exist mainly due to the engagement of individuals according to the department's representative. He viewed the issue of neglected diseases as part of the socio-economic development barriers of developing countries. As such, the topic should be considered as an important field within development cooperation. However, he expressed his disappointment that the problematic of neglected diseases does not sustain a continued interest and commitment within his Agency and the Ministry for Foreign Affairs, and concluded that programs might run out with the end of the personal engagement.

[339] *See* paragraph 3.b).

c) Intellectual Property: Swiss Federal Institute of Intellectual Property (IIP) / Technology Transfer Office of a Swiss university and related university hospitals

(1) Swiss Intellectual Property legislation

According to its dedicated mandate, the contribution of the IIP to the R&D issues for neglected diseases remains focused on IP related subjects. In this respect, the representative of the Institute referred to the adaptation of the Swiss patent system in a way that facilitates research. The 2007 patent law revision introduced several research promoting provisions. One example is a broad patent research exception rule that the representative described as the largest in industrialized countries. It allows the use of the patented invention for reasons of gaining information on the invention independently of additional commercial intentions. In addition, the scope of the patentability of biotechnological inventions, the genetic sequences respectively, has been limited to the necessary sequence of the gene performing the described function in the patent application. Addressing the access to health products problematic the Swiss patent law introduced the possibility to authorize compulsory licenses for exportation to developing countries, according to the newly created conditions defined by the WTO.

Providing funding for the support of R&D for neglected diseases is not within the mandate of the IIP.

(2) University licensing

Switzerland does not have a federal legislation and policy on technology transfer of university innovation. The protection and valorization of inventions is left to the technology transfer offices of universities, and so are licensing policies regarding new developments. As an example, the interviewed technology transfer office of one Swiss university and its related hospitals does not have specific policies in place for new technologies concerning developing countries. Nevertheless, in awareness of the neglected diseases issue and of the discussions about social or humanitarian licensing, the office is working on developing a licensing practice

considering social responsibility in the cases of innovation that relate to resource-poor countries. Such an agreement could, for example, include a clause that obliges the licensing partners to sell the product deriving from the licensed technology to developing countries under a price adapted to the economic situation in those countries. Another strategy to support the valorization of inventions with developing country relevance mentioned by the representative is to file patents for innovation that in general has little markets, however, is funded by considerable philanthropic and public subsidizing structures, such as in the case of neglected and orphan diseases. Here, the technology transfer office considers patenting in order to provide the scientists a background for funding negotiations with potential partners to further develop the inventions into a commercial product. The representative, however, noted, that licensing policies can differ from one technology transfer office to another and will also particularly depend on available budgets of the agencies.

d) Basic research: Swiss State Secretariat for Education and Research (SER) / Swiss National Science Foundation (SNF)

(1) Swiss research policy

The development of science policy and the general coordination of research fall under the remit of the State Secretariat for Education and Research (SER). Its mandate also includes the promotion of higher-education institutes and fundamental scientific research; funding of research institutions outside the university circuit, for example the Swiss Tropical Institute (STI); and the funding of the participation in European programs. The Agency further provides the competitive funding for basic research through the channel of the Swiss National Science Foundation (SNF).

Switzerland has a **general science policy**. This includes a non-specific and non-thematic approach of funding science; the research investment policy is non-sectorial, providing funding on a "common pot" basis for all sectors. It is different from the sectorial approach as established, for

example, in the USA, where each government sector receives funds for research and can link policy with the research subsidies.

Education, research and innovation are extremely important for the social and economic development in Switzerland. The objective of science and research policy is the promotion of excellence, which is also reinforced by the small size of the country, as the representatives noted. Funding of **special research programs**[340] remains limited, in order to ensure high quality research. Special programs risk mediocrity because funding is provided to few researchers without the possibility of ensuring high quality research through competition of other groups and scientific activities.

Following this approach of a general policy of science, Switzerland's research strategy and funding was described as neutral in matters of diseases and projects to be funded. Neglected diseases fall under the common research and science policy and there are no specific initiatives and programs to address the R&D issue. The currently employed general research promoting instruments include, foremost, the competitive funding process of the SNF; the creation of special policies for research areas of great interest; mandates for specific topics[341]; setting up of specific re-

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[340] Examples of special programs that were mentioned:

(1) The Swiss AIDS program, a special financed program that was stopped in 2000 and was integrated back into the SNSF framework because the first products for the disease were on the market, which transformed AIDS into a "normal" disease.

(2) The research on the AIDS cohort studies (evolved out of the Swiss AIDS program). This program has been continued and was described by one of the best in the world. About 4000-5000 patients are in the cohort and have been followed for 20 years. They get tested with the new products that are launched. To continue the study, the SER created a new instrument for the SNF.

(3) The fund of CHF 50 million provided to the SNSF for "Spitzenmedizin", a program initiated to push university hospitals to specializing in a few fields. This special fund is freely administered by the SNF.

(4) Special research policy for cancer for children. Two networks had been funded for clinical trials for optimization of drugs that already exist. Application to children has been on the test, which usually lacks because of the high risks. Another test was the comparison on standards versus the new treatments. The industry generally tests only new treatments versus placebo.

[341] A case example is the Program on research on the safety of nano-materials in Switzerland.

search institutions; establishment of national research programs for areas of major political or scientific interest; grants in form of subsidies provided by the SER for research projects driven by individual investigators. Neglected diseases fit in all frameworks and in none, as the government officials noted. They admitted certain limitations in the application of the traditional R&D promoting instruments to the area of neglected diseases. Firstly, depending on the scope of the definition of the diseases, there might be a lack of competency of the SER. If neglected diseases concern predominately resource-poor countries, the issue would fall under the responsibility of the SDC and related initiatives under development aid rather than research funding. Secondly, the problematic of neglected diseases has politically never been of such importance in Switzerland that the SER would have had to initiate a special research program, or develop a special policy to support R&D in this field. Thirdly, there are currently no policy instruments available within the legal framework of the SER to support PDPs or multinational R&D initiatives and programs focused on neglected diseases. Participation in international initiatives, international or supra-national programs that have not been reinforced by the SNF requires the implementation of these agendas into the existing policy instruments. In this case, problems arise particularly because of the difference between the general science and funding policy in Switzerland and the often thematic approach of international programs. Moreover, the legal framework under which the SER operates does not provide the structure to reserve money for special cases of contribution, as for example for PDPs, or the participation in existing extra framework initiatives. Last, in more general terms, there is a lack of policy instruments to support applied research. All sciences, including the R&D field of neglected diseases, face a fundamental gap of finances between public research funding and private sector funding. In fields such as information technology, the gap can be bridged, for example by venture capital. This financing mechanism, however, does not exist in the field of R&D for neglected diseases. Here, the gap has been taken up by philanthropic foundations such as the Bill and Melinda Gates Foundation (BMGF) and the PDPs, as the government officials noted.

In its position, the SER remains reactive in the support of neglected diseases R&D. The current interactions of the State Secretariat within this field include, according to the representatives, the financial support of the Swiss Tropical Institute; the general funding of the Ecole Polytechnique Fédérale of Lausanne (EPFL) that established and basically finances the Global Health Institute by its global budget; financial contributions to the establishment of the Foundation for Vaccine Development in cooperation with the BMGF; and initiation of the Swiss participation to the EDCTP. A possible implementation of special programs or actions was made dependent on the WHA Global strategy and plan of action (GSPA), the outcome document of the IGWG negotiations that were ongoing at the time of the interview. If they are defined clearly enough, the measures related to the promotion of research, such as the updating of national data bases for ongoing research for neglected diseases, could be used to consider putting the proposed elements into national practice where appropriate, to adopt structural changes in the funding system, to make arrangements on policy level to be more efficient, and to provide additional finances for neglected diseases research. If instruments suggested in GSPA do not exist in the Swiss research framework it would be the role of the SER to consider promoting the establishment of special actions, for example the creation of a special program for neglected diseases within the structure of the SNF. This, however, requires following the regular administrative process, including steps such as stakeholder involvement and discussions, consultation with other departments, and the agreement on the administration level and government level on the initiative.

(2) Swiss basic research funding

The SNF is the single most important institution for basic research funding at national level in Switzerland. Its main goal is to support independent investigator-driven research in all disciplines performed in the country. In accordance with the general Swiss science policy, the objective of the SNF is the promotion of excellence of the Swiss research.

The major part of research grants is assigned to so-called free research that has no thematic approach. Applications have to pass a peer-reviewed competitive process. The evaluation of the applications is based on criteria such as the scientific importance and actuality of the project; its originality; the choice of methods; and the scientific competence of the applicant.

At a much smaller level, the SNF further employs a targeted research program that is problem-oriented and limited in time and funding. The topics are specified by the Government based on their national importance. Through the channel of the SNF, Switzerland also participates in international research frameworks or enters bilateral research cooperation with selected countries. This includes the EU framework research programs and membership in the European Heads of Research Councils (EuroHORCS), as one important research policy making platform in the European Union.

At present, the Biology and Medicine Division of the SNF supports some basic research undertakings in the field of neglected diseases under its general project funding program and there are no further related special initiatives or policies. The grants were provided according to the commonly applied evaluation criteria. Together with the SDC, the SNF also manages and subsidizes the Swiss participation to the EDCTP.

To promote more research in neglected diseases, the respondents suggested the funding mechanism of the national research program (NRP) as part of the SNF funding framework that supports targeted research. Generally, proposals of topics for a NRP can be submitted by various stakeholders, including organizations and researchers. Decisions on the topics are taken by the Federal Council. Programs run for four to five years and research budget is limited up to 20 million CHF. Funding allocation for research projects related to a NRP is competitive. Another proposal of promoting neglected diseases R&D included a rather indirect approach using the channels of the European collaboration programs. As an example, the representatives referred to the initiation of a EUROCORE program. A strong transnational scientific community in Europe could promote the neglected diseases subject and propose the es-

tablishment of such a European program. This scheme enables researchers to work in joint research projects with scientists in other European countries. Funding for the undertakings is provided by the national agencies, such as the SNF. The European Science Foundation, of which Switzerland is a member, evaluates the program proposal and would engage the SNF if Swiss research is integrated.

e) Regulatory process: Swissmedic (Swiss Agency for Therapeutic Products)

The Swiss Agency for Therapeutic Products has a strategy for international cooperation that, however, does not contain a policy dedicated to neglected diseases. The strategy includes agreements with other national regulatory agencies based on mutual recognition that may cover Good Manufacturing inspections, Good Laboratory Practices with the goal to reduce technical barriers to trade; furthermore, an exchange of information in forms of memoranda of understanding is foreseen with other countries. One part of the international strategy is the cooperation with developing regions, in general, through the channel of the WHO. In this respect, Swissmedic performs training activities for developing countries' delegations and groups[342]; provides assistance to the WHO Prequalification Programme, and quality control activities at the Agency's official medicines control laboratory; involves the Agency's experts in the development of WHO's standards and guidelines; and participates in the International Conference of Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use on behalf of the European Free Trade Association (EFTA).

[342] Swissmedic does not offer regular basic training courses on annual basis with fixed dates but provides the programs on request of the international organization for developing countries' groups on general introduction to the work of the regulatory agency or on specific topics according to the needs of the developing countries' representatives. The training courses are free of charge for the participants or funded by WHO. The representative viewed this approach as advantageous due to its flexibility and adaptability to the interest of a specific delegation or country.

As contributions to the support of neglected diseases R&D, the authority's representative emphasized the general preparedness of the Agency within its possibilities, competences and resources, to provide procedure or scientific advice to stakeholders, including PDPs or companies involved in the R&D for resource-poor countries. Although the Agency does not have a specific formal procedure equivalent to the Article 58 of the European Regulation No. 726/2004[343], stakeholders may request assistance in the market authorization of neglected diseases products in Switzerland. In addition, the Agency will continue with the training programs for developing countries' regulatory authority personnel.

In more general terms, the Agency's representative identified several challenging topics that concern regulatory authorities in developing countries, including lack of basic regulation or its implementation; lack of capacity and financial resources; lack of expertise; counterfeiting products; and difficulties in the distribution of products to the patients. To address these issues, and enhance and accelerate the access to safe and quality products the representative suggested, among others, the creation of regional networks of regulators, such as the Gulf Cooperation Council for Regulators as matters of regional harmonization initiatives to facilitate the registration procedure; the continuation of harmonization of technical requirement for registration of products at international level; the twinning model of the European Union[344]; the consideration of other regulator's decisions in order to avoid duplicating efforts and waste of resources, for example by the introduction of a simplified procedure such as implemented in article 13 of the Swiss Law on Therapeutic Pro-

[343] Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (consolidated version; 6/7/2009). Available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf, accessed on 18 September 2009.

[344] Within the twinning model of the European Union, an older member State generated a partnership with a candidate member. Together they developed the regulatory authority of the candidate State to the standard of the European Union. According to the proposal, this model could be applied as a global system including two or three developing countries. The WHO was suggested as forum to further develop the system.

ducts[345]. The establishment of international cooperation was also considered as particularly important, be it in form of memoranda of understanding, exchange of information or expertise. To address the issue of counterfeiting products, the representative proposed as a short- or medium-term initiative to concentrate on market surveillance instead of the establishment of national market authorization systems, which rather constitutes a long term goal. Presently, the focus of even the least developed countries is on the establishment of capacities for marketing authorization. This does not provide the most efficient way to make use of scarce resources, in the assessment of the Agency's representative. Firstly, the setting up of a fully staffed regulatory authority for all therapeutic areas in certain countries may not be achievable. In addition, the number of applications in developing countries may remain rather small, which questions the immediate importance of a completely equipped regulatory agency. The representative referred to the experiences of Switzerland as a small country that is also expected to develop creative ideas for the optimal use of accessible resources. This leads to considering the expertise of other marketing authorities, the use of reference countries, and bridging procedures for marketing authorization if an approval has been obtained in one or more of these reference countries.

4. Intergovernmental and international collaboration

Key officials considered Switzerland's role in international forums, particularly during the IGWG process, as proactive and progressive. The country had been involved in negotiations to create the CIPIH Commission in 2003, and had also co-funded the resulting report. Moreover, the Commission was chaired by Ruth Dreifuss, the former President of the Swiss Confederation. In consideration of this "positive heritage", Switzerland was interested in applying the results of the CIPIH report in practice, according to one respondent. He emphasized the great impor-

[345] Under Article 13 of the Swiss Law on Therapeutic Products, the Swiss Agency for Therapeutic Products is required to take into account the results of tests for an approved medicinal product that have been carried out by another country having equivalent medicinal product control.

tance of the process itself that raised high awareness of health issues in developing countries and the need to address them, as well as sensitized participating stakeholders at all levels for the underlying issues such as the interrelation between public health, innovation policy and development cooperation. At the international level, the country tries to balance the maintenance of the IP system as the principle incentive in the pharmaceutical sector, with access to essential medicines in developing countries. Within the area of R&D the country seeks to mobilize R&D for neglected diseases in industrialized regions and related capacity building in the resource-poor countries.

In its proactive position during the IGWG process, Switzerland also co-hosted an informal meeting with Brazil, Norway and Kenya in order to find ground for solutions in the negotiations. The key officials involved in the international agendas pointed to the good collaborations between various country groups, including emerging countries such as Thailand or India.

Developing its position in the cross-departmental group between all concerned agencies allows Switzerland to take a coherent position on all aspects involved in the neglected diseases problematic and in the different international panels. The coherency between the standpoints of the trade and the health agencies is particularly important.

However, this proactive role of Switzerland in policy coherency and solution finding is limited by its reluctant position in terms of legal changes and financial contributions, as the key representatives admitted.

5. Evaluation of incentive mechanisms

In general, the interviewed representatives were not familiar with all of the presented incentive concepts or did not feel competent enough to evaluate all the models. Most of them agreed on the importance to have both push and pull incentives, ideally a "basket" of incentives. The creation of a sustainable market for the pharmaceutical industry was viewed as essential to encourage the development of health tools for neglected diseases.

As a general opinion, one official emphasized the need of optimization throughout the whole innovation cycle from discovery to delivery of the developed health tool. He felt that the overall discussion on incentives was too much focused on IP and expressed the need to open up and broaden the debate.

Another respondent pointed out that it ultimately depends on the financial resources that the international community provides to support increasing R&D efforts in neglected diseases. Due to lack of financing contribution, a discussion about the investment in interesting instruments to encourage R&D initiatives remains unsatisfactory.

In evaluating the presented incentive mechanisms, the **patent extension** was viewed as an interesting commercial stimulant for the private sector. However, the barriers for its implementation highlighted by the government representatives were consistent with those of the other stakeholders over the lack of political acceptance on both national and international levels, and the lack of a social contract of the model. The consumers in industrialized countries would have to pay more for important medication for a certain period in order to finance the R&D for neglected diseases, as one respondent noted.

One representative refused the **patent buy-out** model, arguing that it does not make sense for the Swiss Government to buy a patent, particularly because it is not within the competence of the State to develop and market a medicinal product. Moreover, stakeholders, such as PDPs, that are interested in an innovation may get a voluntary license or a royalty free license on the related patent.

Most representatives did not evaluate the **prize fund model** or the **APC** scheme. One key official, however, acknowledged that both proposals address the market failure in the field of neglected diseases. He emphasized the importance to design schemes in a way that they create a sustainable market for the pharmaceutical companies. Moreover, he referred to the need of having several donor countries contributing to a prize fund or an APC in order to guarantee the sustainable financing.

One participant opposed the **PRV** model as possible incentive scheme in Switzerland. He argued it provides an award on another product than the developed neglected diseases drug. The incentive should be on the product itself and not transferable. Thus, he argued that a fast track and priority review for the neglected diseases product itself would be preferable. Moreover, the PRV scheme does not create the same incentive effect for all firms but rather benefits MNCs that consider having a potential blockbuster in the pipeline. This creates the impression of an unequal treatment, as the representative noted. The fast track and priority review procedure requires the fulfillment of specific prerequisites and applies to certain products such as medicine for life-threatening diseases where no alternative treatments exist at all. Providing the accelerated process as option for other than life-saving health tools takes away resources for the fast track and priority review application that are really necessary. The representative further emphasized the limited capacities of the Swiss regulatory agency in terms of finances and personnel and referred to the potentially higher volume of resources at the US FDA. He also doubted the commercial value of the gain of time provided by the accelerated procedure. The fast track approval for a potential blockbuster drug would mean a shorter approval time of two or three months. Looking at the total development time of a new medicinal product this gain of time would be almost negligible.

Another respondent viewed the PRV as potential model for the European region with a participation of Switzerland in the program.

No support was expressed for the **Medicinal R&D Treaty**. The main reasons for opposition were the complexity of the mechanism and the lack of political realism. The issue of R&D for areas of need, such as neglected diseases, requires an immediate program of action and not a discussion on a – at the moment – too theoretical proposal, as one official argued. For another respondent, the debate around the R&D Treaty deals with the question whether it is good to leave all the R&D decisions to the market-oriented pharmaceutical companies, or whether it is preferable to give the decision competence to the State. In accordance with other respondents he, nevertheless, declared that there are currently

other more feasible ways to address global R&D issues. Presently, the trend is less rules, less regulation, more freedom for the private sector; not the contrary. This includes particularly creating incentives that address the current market situation. As one official joining his opinion noted:

> "If you look at the development within the last 100 years, then the pharmaceutical industry has not done such a bad job. If you say maybe the basic principle should be a free economy and then you identify areas where it does not work, you find a program on the neglected diseases. And you get the free market to invest in these incentives. […] that would be easier to handle than a treaty covering R&D, medicinal products, diagnostics and medical devices for all markets."

For most representatives, however, the R&D Treaty represents an interesting model in the long term.

As additional incentives, participants viewed as important those schemes that facilitate the research process, such as **patent pools** for essential inventions, **access to compound libraries** of pharmaceutical companies, and incentives to encourage basic research. Another proposal was the establishment of a **fast track and priority review procedure for neglected diseases products.**

As a possible pull mechanism, some respondents suggested a **drug purchasing agency** for products for neglected diseases.

Apart from R&D incentives, respondents emphasized the need for education and training in developing countries and **North-South training programs in various fields**, such as clinical trials, public health and others**,** as valuable contribution to address health issues in developing countries.

One respondent viewed as very important that developing countries commit to neglected diseases R&D, declare the intention for advancement in this field and the use of developed products for the health issues in their countries, in their national health and development plans. Articulating this agenda for neglected diseases helps identify potential markets to the private sector, and identify the need for foreign aid if funding is lacking to achieve the politically declared goals. As the official noted:

> "If we would have our partner countries expressing a need for this research as part of their policies […] then we would create a global need for R&D. At the moment research is not high on the agenda of our agency. But on the other hand, we do not have clients neither, countries that actually stipulate need for this R&D in their own development plans."

Finally, participants emphasized the urgent need to create incentives for the **establishment of distribution systems** in developing regions, the development and provision of diagnostic tools, and for the **education of health personnel**. The creation and implementation of **preventive programs** were also highlighted as an important factor in addressing the health issues in developing countries.

The participants expressed no need for creating a national or international legislative framework including market incentives for neglected diseases similar to orphan drug regulations or the Kyoto Protocol. Key officials referred to the GSPA as providing the realistic ideal of required action points to address the health issues in developing countries. They acknowledged the soft law character of the outcome document of the IGWG negotiations as one framework solution at the present moment. However, they emphasized the importance for the WHO member States to implement the whole GSPA and not to just select incentives or action points that are convenient or easy to apply.

6. Product development partnerships

Overall, the respondents acknowledged the importance of PDPs in the R&D process for neglected diseases and their contribution to the significant changes in the R&D landscape for the epidemics affecting resource-poor settings. They perceived the existence of the not-for-profit organizations as a stimulating factor to involve the private pharmaceutical sector into the product development process, but also to push governments to engage in these partnerships, as one respondent noted. Moreover, successful collaboration examples between PDPs and private sector firms would demonstrate the efficiency of this model, which further increases the chances of governmental interest and participation. In this respect, the partnership between Sanofi Aventis and DNDi for the development of a malaria product was mentioned as a very positive illustration.

One representative emphasized that the R&D environment in the developing countries is not prepared to perform the needed health tool development. Thus it would be important to try to pull the private pharmaceutical industry in industrialized countries back into neglected diseases, by looking at market principles and conditions. He declared the model of partnerships as the way forward to deal with the public health issues immanent in developing countries.

> "We cannot longer do it alone or by single institutions. We have to deal with what we have. And what we have here in terms of active compounds and candidates is a certain research advance. We should work with this one. That we can only achieve in partnership. We need private industry, universities and research networks to deal with this, to advance fast enough. It has become obvious that this is the way to go."

C. Results and implications

Overall, the interview responses reflect the complex environment that surrounds neglected diseases, as well as the global policy debate in this

field. Some of the main results may also be well represented in previous studies[346]. Findings should be considered in the context of the limitations of the analysis. Our study concentrates on the perceptions of the various interviewed stakeholders. Our goal was to depict a multiple stakeholder evaluation of the main topics currently discussed in the field of R&D for neglected diseases, as well as identify policies for solutions in general, but particularly for Switzerland. We aimed at receiving a diversity of standpoints across the actor groups, providing a multi-faceted view of the imminent issues.

I. Definition of the term "neglected diseases" and related R&D issues

The definition of the term "neglected diseases" is a field of diverging opinions. While some stakeholders take a very broad approach including all diseases that are not addressed by appropriate tools for prevention or treatment independently of their geographical location or affected population, others emphasize the need to limit the term "neglected diseases" to tropical infections that are not prevalent in industrialized countries but affect poor populations. Proponents of the latter definition disagreed on whether to include tuberculosis and malaria as "neglected", particularly because of the high international attention and financial resources these diseases receive.

Beside their own definition, the study participants generally also used or were familiar with the language provided in the report of the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH), referring to Type I, II, and III diseases with the last two areas as the "neglected" and "most neglected" respectively. This classification of the diseases was considered by all interviewed parties as an appropriate and useful "working definition".

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[346] For example, LSE Report, 2005; CIPIH Report, 2006; or Caines K., Global Health Partnerships and neglected diseases, DFID Health Resource Centre, GHP Study Paper 4, 2004; CIPIH Report, 2006.

The existing "neglect" of product development was basically linked to two aspects: first, the limited financial capability of the affected population that results in little or non-existing pharmaceutical markets in endemic regions. Without commercial incentives the pharmaceutical companies are reluctant to invest into product development. Industry respondents considered the decision to focus the R&D investments in profitable areas as part of the traditional business consideration of commercial entities. For the group of advocacy, on the contrary, it demonstrated the overall malfunction of the pharmaceutical market model and its underlying IP-based innovation system as a whole. Secondly, the "neglect" of certain diseases was also attributed to the lack of political commitment in (L)DCs to seek solutions for their own health problems, as well as in the industrialized countries to promote R&D performance also for diseases not prevalent within their own territories.

II. Motivational and dis-incentivizing factors for neglected diseases R&D performance

In the assessment of all stakeholders, the R&D performance for neglected diseases has significantly increased within the last ten years, resulting in a larger neglected diseases R&D portfolio and higher involvement of a variety of stakeholders, including the private sector, academia, governments, and philanthropic funding agencies.

1. Motivational factors

The motivations to conduct research and product development in the field of neglected diseases vary, depending on the stakeholder within the actor group of producers.

a) Pharmaceutical companies

The engagement of pharmaceutical companies in the neglected diseases area has steadily increased and all industry representatives expressed the willingness of their firms to continue and expand their involvements.

Evidence shows that multinational companies (MNCs) perform neglected diseases R&D or contribute to it for other reasons than the traditional business considerations, such as expectation of immediate return on R&D investments. According to the interview answers of the industry representatives, the following motivational factors could be identified:

- Historical involvement in the field of neglected diseases R&D;
- Long term business considerations in (L)DCs[347];
- Scientific synergy effect of the neglected diseases R&D for commercial diseases;
- Reputational gain;
- Corporate Social Responsibility reasons;
- Strong in-house motivation for the companies' employees.

The interviewed companies that are not actively involved in the R&D for neglected diseases left the field because they did not consider infectious diseases as potential markets and within the business strategy, which implies focusing on the firm's profitable core areas. The lack of an interesting neglected diseases R&D portfolio was another vital aspect. In their clear statements, those companies' representatives emphasized that there are no commercial incentives that would motivate their firms to get back into the R&D for neglected diseases.

b) Product development partnerships

The interviewed PDPs are driven by public health issues. Their motivation to perform neglected diseases R&D is the recognized lack of safe, af-

[347] In the view of the interviewed company actively involved in neglected diseases activities, neglected diseases constitute a long-term business case in terms of sustainability of the pharmaceutical business and growth of markets in now impoverished regions. Investments and involvement in these countries generate advantages for future business relations and strategies.

fordable, high quality health technologies for (L)DCs. The not-for-profit organizations were established because of the recognized lack of health tools and reluctance of the commercial pharmaceutical entities to invest in the unprofitable field of illnesses affecting disproportionately resource-poor countries.

c) Public Research Institutions

The main motivational factors to perform the research in the field of (tropical) infectious diseases for the public research institutions (PRI) are the importance of the addressed health issues and the scientific interest in infectious diseases. Although aspects such as increased awareness and activities of other stakeholders in the neglected diseases area, as well as the augmented financial resources are not the driving reasons, they nevertheless, essentially support and contribute to the research initiatives of the institutes.

2. Main difficulties and dis-incentivizing factors for the R&D

The main disincentives and challenges (besides lacking markets) that were mentioned by the industry respondents are:

- Difficulties in performing clinical trials in developing countries stemming from lack of in-house developing country experience as well as the challenging environment in the resource-poor regions;
- The cultural divergence between industrialized countries and developing regions;
- Insufficient or lacking distribution infrastructures in endemic countries;
- Lack of government commitment in endemic and industrialized countries.

The last four dis-incentivizing factors and difficulties in the neglected diseases R&D performance were also emphasized by the other stakeholders within the actor group of producers, respectively the PDPs and

PRIs. However, as an additional aspect these two groups included intellectual property (IP) and licensing policies of other stakeholders as other experienced and potential hindrance slowing down or, in rare cases, completely inhibiting the R&D process in neglected diseases.

III. Assessment of product development partnerships

The important role of PDPs for increased neglected diseases research and product development was emphasized by all interviewed stakeholders. These organizations have helped to create a product pipeline for neglected diseases and to stimulate various actors, particularly the pharmaceutical industry sector and funders, to engage into the R&D process in this niche area.

1. Advantages of the product development partnership model

For the public sector, PDPs provide a product development model outside the industry model. R&D performance of PDPs appears to be significantly more cost-effective. Their not-for-profit approach and their financing by public and private funding allow the organizations to perform the R&D without considering market dynamics and profitability aspects. Their research focus is on the developing affordable health tools in therapeutic fields of importance for resource-poor regions with a product design adapted to the (L)DC environments. Moreover, in their IP strategy, PDPs consider the issue of affordable access to the developed health products from the beginning of the innovation process. They also often employ a policy that includes knowledge sharing, technology transfer, and capacity building in (L)DCs. Their ability to join capacities from various sectors such as industry and academia and their potential cost effectiveness may encourage funders and policy makers to invest in R&D of products for neglected diseases.

PDPs provide certain advantages, as well as skills, that meet the needs and interests of MNCs performing R&D in neglected diseases. This includes particularly the funding provided by the not-for-profit organiza-

tions, representing the main advantages of collaboration. It allows MNCs to work in and finance the substantially less expensive early stage drug discovery and to get funded for the cost intensive late stage product development, hence significantly reducing the R&D expenses of the firm. Moreover, it distributes the risk associated with pharmaceutical R&D to multiple partners. PDPs further combine private sector and public sector skills and knowledge that enables them to act as brokers between their various partners. With public health staff members from developing countries they offer an expertise in areas where MNCs lack knowledge and skills, including clinical trial performance and regulatory authority processes in endemic regions. In this respect the collaboration with PDPs also provides a learning effect for MNCs. In addition, MNCs receive access to the PDPs' developing country partners and can build relationships in expected future markets.

2. Policies and incentives to support the R&D of product development partnerships

Based on areas of needs and gaps within the product innovation process from basic research to delivery, we identified the following policies and incentives to support PDPs' R&D performance, in general and in Switzerland:

a) Increased government commitment of both (L)DCs and industrialized countries to tackle public health problems in resource-poor regions and particularly the issue of neglected diseases. This includes increased governments' interest in and validation of PDPs' R&D performance to better understand, assess and monitor the success of structure and business model.

b) Increased and sustainable funding as key factor to ensure and increase PDPs' R&D and to provide more credibility for potential partners. This includes:

- Increased contributions of the public sector to broaden the funding base of PDPs. Currently, the philanthropic foundations are the main funders of PDPs;
- The prolongation of public funding commitment for PDPs for several years, instead of the usual one-year period, bringing increased flexibility and credibility for PDPs;
- The creation and support of innovative finance programs, such as an International Finance Facility for neglected diseases or a global fund for (neglected diseases) R&D;

c) The creation of a contact structure for PDPs within the administration that is responsible for dealing with PDPs, in order to prevent a structural void within administration;

d) The creation of incentives to stimulate collaborations and partnering of stakeholders with PDPs, including screening activities and further development stages, for example by tax credits and other incentives;

e) Facilitating access to knowledge at early stage. This could be achieved, for example, by an anticipated regulation of the licensing policy of publicly financed innovation requiring access to developing countries related technology;

f) Sustaining funding for basic research in the field of neglected diseases;

g) Facilitation and support of technology and know-how transfer to (L)DCs.

They further viewed a change of their legal status from a Swiss foundation to the status as an international organization as financial support due to related reduction in VAT payments and taxes to be provided for the PDPs personnel.

Finally, one specific proposal concerns the regulatory process and includes the implementation of a rule in Switzerland similar to Article 58 of the European Regulation No. 726/2004 whereby the Swiss regulatory authorities would be mandated to provide scientific advice to neglected

diseases products and the related approval process. For this the Swiss Government could also provide the required funding.

IV. Incentive mechanisms

The assessment of the pull incentives presented in the interviews strongly captures the global discussion on the advantages and drawbacks of the proposed schemes, as well as the position of the various stakeholder groups on the preferable incentive solutions. Important findings are highlighted hereunder. For a more detailed description, we refer to the respective paragraphs on the evaluation of the incentives of each group of actors.

1. Partnerships

MNCs seem to prefer to partner with PDPs to perform product development for neglected diseases or, at least, are prepared to contribute to the R&D projects of the not-for-profit organizations. This includes both firms directly involved in R&D activities, as well as those that have left the infectious diseases field.

The advantages of PDPs for the private sector have been summarized above[348]. PDPs were seen as the most effective way of encouraging MNCs to conduct R&D for neglected diseases by all industry representatives, and by other stakeholders. Currently, most related R&D projects are carried out in collaboration with PDPs.

2. Incentive mechanisms

a) Proposed pull mechanisms

Overall, it appears that none of the presented commercial incentive proposals will stimulate MNCs to start a complete in-house R&D process on neglected diseases from discovery up to the marketing of the developed

[348] *See* paragraph II.1.b).

product while abandoning a core commercial field. This is particularly based on the opinions we received from the pharmaceutical industry representatives, and is also reflected in the responses from the PDPs and the advocacy groups. The potential returns provided by the mechanisms are expected to be much smaller than the value of the commercial market. Further, the incentive proposals do not sufficiently solve the high uncertainty that pharmaceutical companies face in their R&D investment decisions because of the high costs and risks of the drug development process.

The presented pull mechanisms, may, nevertheless, be important additions to the current business model of the pharmaceutical industry and the multi-sectoral partnership approach in serving the following vital functions:

- Influence a (multinational) company's decision to continue with its neglected diseases R&D portfolio that would otherwise be abandoned;
- Encourage the in-house development of modification or adaptation of an existing product for neglected diseases indications;
- Encourage the neglected diseases R&D performance of (multinational) companies that may be able to create scientific synergies with their commercial business fields;
- Encourage multinational companies to partner with other stakeholders, particularly with PDPs;
- As incentive for emerging countries' pharmaceutical companies to add neglected diseases to their R&D portfolio.

(1) Advanced Purchase Commitment (APC)

The Advanced Purchase Commitment (APC) was perceived by most stakeholders as the most attractive mechanism in comparison to the other models, particularly because of its compliance with the business thinking of the MNCs. Main drawbacks were design issues, such as addressing the "second mover" problematic or the question of credibility of

donors' commitment. It was emphasized, however, that the scheme would rather serve as an agenda for companies with already existing neglected diseases portfolios or for cases of product adaptation of existing drugs for other (neglected) diseases.

(2) Prize fund

The prize fund proposal provides a further accepted incentive option. However, it received less approval in comparison to the APC by most stakeholders, besides the advocacy groups. The scheme was perceived as less in line with the pharmaceutical business model. Further main disadvantages associated with the prize fund were the requirement of advanced R&D investments and the high uncertainties to recoup R&D expenses. In addition, it appears that the scheme carries the burden of not having found its practical application in the pharmaceutical R&D field so far.

For advocacy groups, the prize fund presented the preferable incentive mechanisms as addition (or alternative) to the patent system. The mechanism provides both a financial reward for the product developer based on the health impact of the product and a reputational gain while at the same time separating the development costs from the price of the end product. It can also be designed without exclusivity rights to allow immediate access to knowledge and facilitated technology transfer. Other mechanisms were seen as less effective in terms of required costs and access.

(3) Priority Review Voucher

Furthermore, strongly influenced by its implementation in the United States, the Priority Review Voucher was discussed as potential incentive scheme. Main drawbacks are the ethical considerations related to the use of the regulatory process as incentive vehicle and the possible impediment of the accelerated approval of life-saving products.

An implementation should be effected at European level with the participation of Switzerland in order to offer a strong incentive. The efficiency of a realization in Switzerland alone is doubtful because of the small market the country provides. Moreover, financial and human resource capacities at the Swiss regulatory authority are limited in comparison to the FDA or the EMEA.

(4) Transferable patent extension

The proposal of a transferable patent extension was refused by all stakeholders. Although in theory an attractive scheme for MNCs, it lacks political feasibility and distorts the market.

(5) Patent buy-outs

The mechanism of patent buy-outs basically appeared too theoretical. Instead, a favorable licensing practice of patent holders concerning technology for (L)DCs was seen as better option.

(6) International Medicinal R&D Treaty

The Medicinal R&D Treaty was opposed by the pharmaceutical industry as obstacle to the market model and as too bureaucratic, thus inhibiting the flexibilities that the current market-based innovation system provides. Most other stakeholders agreed on the still too theoretical stage of the treaty proposal and referred to the need of an immediate and medium-term solution to encourage and increase R&D for neglected diseases products. This includes particularly the establishment of market-based incentives to involve the pharmaceutical industry into the product development. However, if further matured in design and provisions, the treaty might be an option for the future, as the advocacy and the regulators group concluded.

b) Further push and pull incentives

The interview respondents agreed on the importance to have both push and pull incentives to support and stimulate the R&D on neglected diseases.

Outside the scope of the presented pull mechanisms, the following push and pull instruments were included for further considerations:

(1) Push incentives

- Funding of basic and transitional R&D on neglected diseases;
- Tax credits for activities related to R&D on neglected diseases;
- Proposals related to the regulatory process, including the introduction of a scientific advice procedure for neglected diseases products; the implementation of a fast track procedure for neglected diseases products; fee waiver for the approval process of a neglected diseases product;
- Facilitation of access to knowledge related to neglected diseases related knowledge at early stage, including particularly public research institutions as developers of upstream technology;
- Patent pools

(2) Pull incentives

- Establishment of purchase agreements for neglected diseases products comparable to the GAVI approach in order to address the distribution issue in (L)DCs;
- Establishment of a (Global) Fund for R&D in neglected diseases[349].

The combination of both the push and pull incentives within a legislative framework, similar to the orphan drug regulations, was not considered

[349] For example, as proposed by one pharmaceutical industry representative (described in paragraph B. I.1. d).

as an interesting option. Instead, the GSPA may provide a sufficient framework to develop national strategies on the support of R&D for neglected diseases, including the creation of incentives based on the specific environment of each WHO Member State. Regulators perceived the non-binding legal character of the strategy as facilitating the implementation. Other stakeholders, such as the advocacy group, emphasized the importance of governments' efforts to realize the action points developed under the GSPA to ensure its effectiveness in addressing public health needs of the (L)DCs.

c) Further policy program proposals

Further stimulating factors and policy proposals, beyond the commercial incentives include:

- The promotion of the neglected diseases subject among the various stakeholders in the country and of collaboration and partnerships in this field;
- The establishment of programs that help to improve the clinical trial performance in (L)DCs;
- Suggestions related to the international collaboration in the public health and the neglected diseases field:
    - The promotion of the neglected diseases issue among international organizations, i.e. the development of a favorable position in the international forums; the promotion of the topic among other governments;
    - Governmental commitment to the international organizations and their importance in directing the international collaboration and policy setting;
    - Increased funding for international organizations involved in the public health fields, such as the WHO or the TDR in order to support their expanding activities and responsibilities.

V. Switzerland

1. Current policy on R&D for neglected diseases

The main drawback of Switzerland's policy approach to the global health subject, including neglected diseases R&D, is the lack of increased financial resources for this domain. While other countries doubled and tripled their investments in this field, Switzerland has not increased the budget. This becomes particularly apparent in the field of the **Swiss Development Cooperation**, responsible for supporting international initiatives on global health, and neglected diseases, as well as related R&D projects. The lack of an increased Official Development Aid (ODA) makes it difficult to allocate a share of the basic budget to the health sector in accordance to the importance and present scale of international activities in the domain; furthermore, respective contributions reduce the overall budgets for other essential sectors of Development Cooperation.

Currently, neglected diseases R&D programs and initiatives are integrated into the regular legal and administrative frameworks in Switzerland. The Departments responsible for public health, research and technology, IP and Development Cooperation do not have specific policies in supporting R&D for (L)DC diseases.

From the **public health** point of view the link to infected citizens from travels to endemic countries or infected immigrants to Switzerland is not sufficient to develop a concerted public health strategy. The financial support of R&D initiatives for neglected disease does not fall in the realm of Swiss public health.

Switzerland supports **fundamental science** and translational projects related to neglected diseases[350]. However, the application of the current

[350] One main example is the support of the STI by the Swiss Federal Government, or the foundation of the Global Health Institute as part of the Swiss Federal Institute of Technology at Lausanne. This organization focuses on studies in basic biological mechanisms underpinning infectious diseases research and drug discovery in the area of retro-viral diseases. Some other basic science projects on neglected diseases are funded through the channels of the SNF. These examples of neglected diseases initiatives illustrate the possibility of implementing neglected diseases into the Swiss research, and that neglected diseases related scientific projects can contribute to the excellence of research in Switzerland.

R&D promoting instruments to the area of neglected diseases is limited. Because of lack of concrete political commitment there is no incentive to develop a special research policy for this therapeutic area, or a special research program and to provide respective funding. Furthermore, the current legislative framework does not provide the option to support PDPs or multinational R&D initiatives and programs focused on neglected diseases. Last, there is a general lack of policy instruments to support applied research.

The Swiss **IP** policy aims to promote research[351] and access to health products in (L)DCs[352]. However, the patenting and licensing or technology transfer policy is not regulated at the federal level. The protection and valorization of inventions is left to the technology transfer office of the respective organization, and as such the licensing regarding the innovations. The consideration and implementation of social licensing related to technology relevant to (L)DCs depends on the awareness of the issue at the individual agency and its available budget.

Outside the regular marketing process responsibilities the Swiss **regulatory authority** employs an international strategy that includes collaboration activities with WHO and contributes to global health issues[353].

Implementing strategies to facilitate the use of the less complicated marketing authorization system in Switzerland for neglected diseases products was perceived as supportive for the product development process[354].

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[351] For example, by including a broad research exemption, and limiting the patentability of biotechnological inventions.

[352] For example, by implementing the WTO Decision on Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health of August 2003.

[353] Among others, the Swiss Agency performs training activities for (L)DCs' groups; provides assistance to the WHO Prequalification Programme; and acts as a quality control authority for the WHO. The Swiss Agency intends to continue with the training activities for (L)DCs delegates, thus contributing to the capacity building in these regions and the improvement of clinical trial conditions in (L)DCs.

[354] In some (L)DCs Switzerland is used as reference country, and the Swiss regulatory authority approval may provide certain value in (L)DCs, thus accelerating the marketing process of the neglected diseases products in these regions.

This might require a clearly developed strategy that addresses neglected diseases and the allocation of adequate financial resources.

2. Point of view of other stakeholder groups

Switzerland is perceived as a key country in addressing the lack of neglected diseases R&D according to all interviewed stakeholders[355]. However, the Country does not take an active role in exploiting the advantages of the strong local conditions, which was attributed to the lack of political commitment to address the neglected diseases R&D issue. The main policy options that were raised relate to the implementation of the internationally agreed specific actions of the GSPA, the creation of a structure that links the Swiss based actors in the medical and pharmaceutical field; and the concrete integration of public health issue of (L)DCs into the Swiss Development Cooperation. The latter includes both the concentration on socio-economic development concerns in (L)DCs, as well as the support of medicinal R&D for the resource-poor regions. This may require the creation of an internal structure within the relevant Department that is responsible for (L)DC public health, furthermore, the increase of the Swiss ODA up to the internationally committed 0.7 percent to provide the necessary financial resources.

D. Conclusion

Our study exposes the critical role of product development partnerships (**PDPs)** in the innovation process for pharmaceutical products for neglected diseases.

They are important for the public research institutions that develop the up-stream technology for neglected diseases, but are not further involved in the innovation process. PDPs are likely to pick up the technol-

[355] This was principally based on the excellent medical R&D environment (including the universities, the research institutions, and the academic hospitals and laboratories), the strong biotechnology and pharmaceutical sector, the PDPs and the international organizations situated in Switzerland, and the country's financial capacities.

ogy and conduct the product development by funding and partnering with, for example, pharmaceutical companies. As such, they may fill the gap between discovery performed by the public research institutions (PRI) and translational research.

For multinational companies (MNCs) engaged in the neglected diseases R&D, the not-for-profit organizations provide least developed countries and developing countries ((L)DC) with public health skills that are vital for product development and financial resources to fund the expensive clinical trial phases.

Furthermore, PDPs provide advantages that other incentive models lack. Particularly, their public health focus, their function as broker between various stakeholders, and their involvement in all stages of the innovation process starting from discovery up to the marketing of the developed product, as well as delivery to the affected population, underlines their exceptional role in the neglected diseases R&D. After ten years of existence, the organizations have successfully marketed the first products in (L)DCs. Although their performance, impact and return on investments have not yet been sufficiently investigated, they appear to be a success story and continue to attract the contributions of various public and private sector stakeholders of all sizes, on for-profit or not-for-profit basis, and the attention of those dealing with the underlying issue and urgency of lacking health technologies in resource-poor countries.

The foundation of PDPs has changed the R&D landscape in the field of neglected diseases and they are more and more confirming their position as key actors in addressing diseases that have been abandoned for a long time.

Thus, the support of PDPs should be considered as principal strategy of governments in the development of a policy related to stimulating R&D of pharmaceutical products for neglected diseases.

PDPs need, foremost, a continuous flow of funds that are important to manage the organizations and to provide them with flexibility and credibility in collaborating with other partners. In addition, there is demand for a broadening of the funding base for PDPs. They are still often supported by a single predominant funding source, namely the Bill and Melinda Gates Foundation (BMGF).

Furthermore, PDPs need access to private sector skills and technical expertise, as well as physical resources. An increased private sector involvement would be beneficial for the not-for-profit organizations and should be stimulated by adequate incentives.

PDPs, however, are not numerous and focus on certain neglected diseases, leaving others still uncovered by research efforts. It requires more actors to receive a comprehensive and thorough R&D portfolio in the area of diseases predominately or exclusively affecting (L)DCs.

The Special Programme for Research and Training in Tropical diseases (TDR), the international organization focusing on tropical diseases, will continue to play an important role in addressing the still neglected diseases conditions.

TDR should be further supported by funding adapted to its increased performance and responsibility.

Furthermore, the participation of MNCs and other private sector players is a necessity. MNCs are willing to contribute to neglected diseases R&D under aspects of Corporate Social Responsibility or due to business considerations. Providing commercial incentives may not encourage MNCs to start neglected diseases R&D but may serve other important functions, such as encouraging the firms to continue with neglected diseases R&D portfolios besides their commercial R&D fields. In addition, most health product development does not focus on the development of new chemical entities, but on the adaptation of existing products for other conditions. There are also scientific synergies possible between commercial

diseases and neglected diseases, for example between hepatitis C and Dengue fever. In such cases incentives may stimulate research on product modification or adaptation for the unprofitable condition.

Thus, pull incentives should be part of a strategy addressing the lack of neglected diseases health products.

Our findings indicate that the three **pull incentive models**, namely the advanced purchase commitment (APC), the prize fund, and the transferable Priority Review Voucher (PRV) are the most attractive mechanisms for the interviewed stakeholders, while the transferable patent extension and the patent buy-out scheme are not considered as suitable.

Pull incentives should be completed by **push mechanisms**. The implementation of both mechanisms will be important to provide flexibilities to interested stakeholders and to attract a variety of activities.

Governments will need to choose the incentive options that are best adapted to the national economic and scientific preconditions.

Switzerland plays a key role in the solution to the neglected diseases R&D issue. The country has the unique advantage of having important national and international stakeholders within its territory.

This provides the opportunity to act as mediator between the different groups and to link them, as was strongly emphasized by our interview partners.

Neglected diseases R&D projects and initiatives have received support from different Swiss administrative departments. So far they have been included into the regular activities of each administrative Agency, in-

cluding domains such as research and technology, development cooperation, as well as the regulation of medical products.

Our findings, however, illustrate that the Swiss Federal Administration could improve its coordination and develop its influence in that field.

Switzerland also provides competitive advantages in the medical R&D field, such as the excellent and supportive education and science policy, a high-profile scientific environment, the strong biotechnology and pharmaceutical industry, and the presence of several PDPs on its territory. A more efficient use of this knowledge and intelligence also in the field of neglected diseases R&D requires the development of a committed and concerted strategy.

The WHA Global strategy and plan of action (GSPA) may offer a strong external stimulant to commit politically and financially to the implementation of the necessary actions as agreed in the WHA resolution.

Recommendations

Based on our findings we make the following recommendations for further consideration:

1. The support of public-private product development partnerships (PDPs)

The support of PDPs is the principal mechanism to ensure the continuing and increasing R&D of pharmaceutical products for neglected diseases.

a) Financial support

Financial support is the critical point. It requires increased and steady direct funding of the organizations. Funding should be provided in a longer term commitment for several years to ensure the flexibility and credibility of the PDPs.

New sources of funding for innovation in neglected diseases technologies may be considered and promoted. An opportunity to diversify and increase the funding base at the international level could be the extension of the mandate of existing mechanisms such as the Global Fund for AIDS, Malaria and Tuberculosis to neglected diseases, or the establishment of a fund for related R&D. Furthermore, other funding mechanisms focused on private capital markets (such as an International Finance Facility for neglected diseases) might be considered to generate additional finances.

b) The creation of incentives for collaborations with PDPs

PDPs are dependent on the contributions of other stakeholders, particularly from the private sector. Partnering and collaboration could be supported by tax credits for neglected diseases R&D activities; by research grants for public research institutions (PRIs) for research related to ne-

glected diseases; by the implementation of special programs, for example, within the funding structure of the Swiss Innovation Promotion Agency (CTI) to encourage the transitional science collaboration between various stakeholders from the academic and the private sector and PDPs; or by implementing special programs for the support of PDPs within the structure of the Swiss Secretariat for Education and Research (SER).

c) **The creation of a network structure** within Switzerland to link PDPs to all relevant private and public stakeholders in the biomedical, biotechnological and pharmaceutical sector within the Swiss territory.

d) Facilitating the yearly tax burden of PDPs

This may be achieved by a change of the legal status of PDPs from a Swiss foundation to an international organization in order to enable the PDPs to benefit from the special tax advantages provided to the new status; or by a regulation at the cantonal level in the Canton of Geneva, where many PDPs are situated.

2. Promotion and implementation of push and pull incentives

Push and pull incentives should be implemented to provide flexibilities to interested stakeholders and to encourage a variety of activities of public and private stakeholders involved in the pharmaceutical R&D process in Switzerland.

a) Push incentives

- The consideration of the implementation of **tax incentives** for biomedical and pharmaceutical R&D activities, with particular emphasis on neglected diseases;
- The promotion of **patent pools** for technologies relevant to neglected diseases among public and private sector actors;

- The development and implementation of a federal strategy concerning a **social licensing practice** related to innovations with neglected diseases background, particularly among PRIs, including universities; the promotion of a social licensing practice also among other stakeholders such as pharmaceutical and biotechnology companies;
- The implementation of incentives concerning the **regulatory process**, including the regulation of a scientific advice procedure for neglected diseases product developers; the implementation of a fast track option for neglected diseases products; the waiving of fees related to the approval process.

b) Pull incentives

The promotion of the **advanced purchase commitment** and the **prize fund** models at international level should be considered where appropriate to encourage the pharmaceutical product development for a particular neglected disease. Switzerland should further consider its financial participation in related current and future programs that are implemented at the international level.

3. Support of relevant international organizations

a) UNICEF, UNDP, World Bank and WHO Special Programme for Research and Training in Tropical Diseases (TDR)

The Special Programme for Research and Training in Tropical Diseases (TDR) has been successful for many years in pharmaceutical product development for neglected diseases in partnership with private and public actors. The international organization will continue its activities related to neglected diseases R&D for diseases that are not addressed by PDPs or other organizations. The continuous financial support of TDR will be important for the pharmaceutical product development for diseases of (L)DCs not yet addressed. Projects and activities of the TDR have increased in numbers and funding should consider these additional responsibilities accordingly.

b) World Health Organization (WHO)

The WHO is the health-specialized United Nations body. Neglected diseases are implemented in various programs of the international organization, such as the Essential Medicines Programme, the Prequalification Programme, or various control programs related to neglected diseases. Moreover, after governments, the WHO is the second responsible actor for the implementation of the WHA Global strategy and plan of action. According responsibilities need to be supported financially, and funding contributions should reflect the increased tasks of the organization.

4. The implementation of the WHA Global strategy and plan of action (GSPA)

Switzerland has been pro-active in the processes of the WHO Commission on Intellectual Property, Innovation and Public Health (CIPIH) and Intergovernmental Working Group on Public Health, Innovation and of the Intellectual Property (IGWG) that led to the adoption of the GSPA. The country should continue its engagement by implementing the specific actions of the strategy. It should also develop national strategies in the following areas:

- The promotion of knowledge and technology transfer to (L)DCs among all stakeholders, particularly the private sector actors. This may include, for example, the increased support of exchange programs between Swiss and (L)DC universities; the increase of grant programs for (L)DCs PhD candidates and scientists for studies or research in Switzerland; the further promotion of network structures between Swiss and (L)DCs researchers; and the creation of incentives for the private sector to encourage the transfer of knowledge and technology related to pharmaceutical development or other sectors such as biotechnology.
- The support of programs that help improve the clinical trial performance in (L)DCs, particularly the development of North-South

training programs, by providing grants for the trainings of scientist and health worker of endemic countries.

- The promotion of pharmaceutical R&D capacity building in (L)DCs.

5. Fundamental research

The development of a national strategy to support the continuous basic and translational research for neglected diseases.

This may be of particular importance for Switzerland because of the strong involvements of Swiss public research institutions (particularly the Swiss Tropical Institute, as well as the Global Health Institute) in this research and, the option to increase and further develop excellence within this field. The strategy may contain the development of a special R&D program for neglected diseases within the research and science policy; the development of a national research program under the framework of the Swiss National Science Foundation (SNF); the development of a framework that facilitates the Swiss participation in international programs such as the European and Developing Countries Clinical Trials Partnership (EDCTP); and the consideration of increased support of North-South scientific collaborations related to neglected diseases, for example through the channel of the SNF.

6. Development cooperation

The responsibilities of the Swiss Development Cooperation (SDC) includes the support of the socio-economic development of (L)DCs. Ill health impedes the socio-economic development of both the affected individuals and the endemic countries. Thus, public health issues of (L)DCs, and as such neglected diseases, should be developed in the framework of the Swiss Development Cooperation. The creation of a structure that would be exclusively responsible for (L)DC public health concerns within the Swiss Agency for Development and Cooperation should be considered. Furthermore, the financial resources of the Agency need to be increased in order to contribute to international neglected dis-

eases health programs and initiatives according to their scope and importance (also including in particular the funding of PDPs).

7. Development of a neglected diseases network structure in Switzerland

Switzerland has an excellent medical, biotechnological and pharmaceutical R&D environment. It should develop a strategy to link all actors by creating a network structure of all Swiss-based stakeholders active in the field of neglected diseases to provide them with a platform for interaction, discussion, information and other related activities.

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Neglected diseases face a lack of pharmaceutical products for prevention, diagnosis and treatment. Promotion of innovation in the pharmaceutical sector also needs incentives for the health necessities of the poorest populations. There are various ways to address this objective. The first part of the book examines the recent legal and socio-economic context and developments in the field of neglected diseases, as well as the proposed mechanisms to stimulate research and development of lacking pharmaceutical products.

Where is Switzerland's role in all this? How does the country use its competitive advantages in the biomedical research and development sector to contribute to pharmaceutical R&D for neglected diseases? And, where are areas of possible policy changes or adaptations to better integrate the issue of neglected diseases into the national biomedical innovation environment? The second part of the book tries to find answers to these questions based on a broad consultation with relevant Swiss stakeholders from the pharmaceutical industry, public private development partnerships, non-governmental organizations and government agencies. Conclusions are drawn and proposals are made for a better promotion of the pharmaceutical innovation in Switzerland for diseases predominately affecting developing countries.

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