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New medicines for neglected diseases

Summary

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Summary

Summary

Numerous diseases that rarely occur in highly developed countries or that can generally be treated effectively there continue to lead to far more serious health problems in developing countries. The causes of this are manifold. In addition to insufficient healthcare provisions and other local conditions that require particular product specifications, the structures of the commercialised system of pharmacological innovations in the industrial countries and the international pharmaceutical market are also blamed for this. In developing countries, this results in two interconnected problems: First, numerous activities in research and development (R&D) take place to combat diseases that occur frequently both in industrial and in developing countries. However, as such activities can only be (re)financed for a certain period of time via product prices, high prices prevent poor countries in particular from procuring the required medicines in sufficient quantities and making them available to the population (access problem). Second, for diseases which almost exclusively occur in poor countries, hardly any new products are being developed in the first place, since the cost-intensive research and development cannot be (re)financed through the product prices (R&D problem).

On the basis of the Millennium Goals agreed in 2000, numerous actions to improve the situation were stipulated. Their primary objective is to improve access to available medicines and medical care, but they should also work towards the medical innovation system focusing more clearly again on poverty-related and neglected diseases. It is widely agreed that neither the public sector nor the private sector alone have the necessary capacities to develop medicines to combat diseases that mostly affect poor countries. Views differ concerning the general suitability of the prevalent patent-based innovation system and thus the various measures that have been discussed and also partially implemented in recent years. At times it is noted that the great number of measures results in some confusion and in increasingly complex coordination.

The Committee for Education, Research and Technology Assessment of the German Bundestag has tasked the Office of Technology Assessment (Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag [TAB]) with providing an overview of already established programmes and concepts for the strengthening of R&D in combatting poverty-related and neglected diseases (PRND). This final report looks at the medical innovation system with its product development phases and funding mechanisms and outlines initiatives by public and private R&D actors as well as political measures to increase commitment in respect of poverty-related and neglected diseases. From the comprehensive analysis of the current situation, courses of action for political decision-makers will be

derived in order to counter the R&D problem associated with poverty-related and neglected diseases.

What diseases, what requirements in terms of research and funding? 1.

To date, no standard definition or list of poverty-related and neglected diseases exists. Consistently the term comprises diseases which mainly occur in poor countries and for which commercial companies have not developed any or hardly any new products in recent years due to financially weak demand. Mostly, the so-called »big three« (tuberculosis, malaria, HIV/AIDS), most of the 17 neglected tropical diseases defined by the WHO as well as some respiratory and diarrhoeal diseases are referred to as poverty-related and neglected. All of them are infectious diseases caused by a range of pathogens (viruses, bacteria, protozoons, worms). Some of them transmitted by insects and other intermediate hosts. Especially in developing countries, estimates regarding the spread and health consequences of these diseases often remain vague. The “Big Three” together with respiratory and diarrhoeal diseases remain widespread in developing and newly industrialized countries and cause most deaths in the poorest countries, often already among children. The 17 neglected tropical diseases are often less widespread, cause fewer deaths but are associated with impaired health, disability and social exclusion. Depicting their impact on society with established reporting systems and models remains difficult. Especially diseases that occur very rarely or only locally often do not appear on the radar of global health reporting. Prior to 2014, for example, Ebola fever was not included in any list of neglected diseases.

Experts assess the R&D requirements for the above mentioned diseases individually for each disease and in terms of different product groups and/or patient populations (e.g. medical devices, medicines, pediatric formulations). The need for R&D results from existing knowledge, current options and limitations in combating the respective diseases as well as the respective conditions in the areas where the disease is prevalent. Needs specific to developing countries are in particular identified for insect repellent products, simple and yet specific tests that require no special laboratory equipment, vaccines that require no refrigeration as well as durable, standardised fixed dose combinations of required active substances - and thus hardly any overlap exists with the objectives of the medical innovation system of industrialised countries (personalized high-tech medicine). It is almost impossible at present to provide a realistic estimate of the costs of covering such a need for R&D specific to developing countries.

Case study: Malaria**2.**

Taking the poverty-related and neglected disease of malaria, the report – by way of example – outlines existing options and the challenges arising from them for research and product development. Malaria is caused by plasmodia- single-celled parasites that are much bigger and more complex than viruses and bacteria. Five species of plasmodium can cause malaria in humans. They differ in their regional spread. Plasmodia are transmitted through the bite of infected anopheles mosquitos. When the mosquitos bite to obtain blood, the parasites enter into the human blood circulation, spread, destroy the red blood cells and are transmitted onwards when the infected person is bitten again. A number of different approaches exist in combatting malaria: attacking the mosquitos, human immunisation and killing the plasmodia in the human blood.

Insecticide-treated bed nets and indoor room sprays are used against the nocturnal insects. Bed nets are currently considered the most effective preventive measure. In recent years, large parts of the population in endemic regions were supplied with these nets, with billions in financial support also provided by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). The insecticides have been widely used in agriculture for a long time. Their use in malaria prevention is an application extension. For many years now, agricultural and health organisations as well as the United Nations Environment Programme (UNEP) have warned about the development of resistances as the result of the parallel use of the same substances in both medicine and agriculture. Already the first Global Malaria Eradication Programme failed in the 1960s, among other things because the insecticide used at that time lost its efficacy. The development of new insecticides for combatting disease-transmitting insects is an urgent R&D task.

Even if almost all people in malaria-endemic regions are infected with plasmodia through mosquito bites, Malaria is affecting mostly in those people whose immune systems are insufficiently able to combat these pathogens. First and foremost, these include babies/infants and pregnant women, but also people who are only short time in malaria-endemic regions. Early detected infections can mostly successfully treated with available medicines. However, delays can result in complicated and even lethal progressions. In small children in particular a simple infection can quickly develop into a complicated malaria. At present, the most effective agent for the treatment of malaria is artemisinin, but in some Asian regions plasmodium species are already becoming resistant against it. The WHO generally recommends combining artemisinin with other agents, in order not to encourage the development of resistances. In highly endemic areas, particular high-risk groups of people are often given prophylactic medica-

tion. On the one hand, this may prevent a certain number of infections, but on the other, this dual use also accelerates the development of resistances. For that reason, another urgent R&D task is thus the development of new active pharmaceutical ingredients. Diagnostic tests that are fast, simple and yet as accurate as possible are of the utmost relevance. Currently available rapid tests are not very reliable especially during the early stage of the infection and have as yet been unable to detect resistances to particular medicines. Here, too, an urgent need for R&D exists.

To date, there are no vaccines against diseases caused by single-cell organisms such as plasmodia. An effective vaccine against malaria would be a great step forward.

Since the fight against malaria as one of the “Big Three” has been agreed by the international community to be one of the millennium goals, numerous activities, including multilateral ones, have been initiated in order to support the countries affected by malaria in their battle against the disease:

- › establishment of the Roll Back Malaria partnership for the global coordination of control measures as well as R&D activities;
- › establishment and funding of GFATM that supports malaria-endemic countries in the procurement and provision of available products in sufficient quantities (mainly mosquito nets, rapid tests and medicines), as well as
- › strengthening of basic research and the establishment of various non-profit product development partnerships (PDPs) financed by donations that, in cooperation with private enterprise, search for new active substances and further improve already available medicines (e.g. new combinations of active substances, paediatric formulations).

Despite intensive efforts, the major R&D challenges in the fight against malaria – such as the development of new agents (insecticides, medicines, vaccines) as well as simpler and more accurate diagnostic tools – still remain unsolved. If the medical innovation system of the industrial countries were supposed to contribute to solving these problems, this would involve considerable expenditure, since this system requires strict documentation of evidence of the safety, efficacy and quality of the respective products. This necessitates substantial R&D activities. In the healthcare system of the industrial countries, only tested, licensed and certified products can be used in the treatment of diseases. Even bi- and multilateral programmes with the involvement of industrial countries that aim to fight poverty-related and neglected diseases such as malaria increasingly call for such product certifications.

The medical innovation system – course of action and opening up of procedures

3.

Course of action

3.1

A structured procedure with several sequential and incremental stages of R&D has emerged in order to provide evidence of the safety (potential risks to humans and the environment) and efficacy or reliability (in relation to disease-specific conditions). Any development of a medicine is scientifically based on detailed knowledge of the causes of the disease and of disease-related processes within the human body (basic research). The subsequent product development requires an increasingly structured and formalised approach that also needs to include economic considerations. During the early stages of the development process, numerous substances are tested, applicable and producible candidates selected and developed further as well as first safety questions answered (during the so-called preclinical stage with the aid of cell cultures and animal testing). Following the successful conclusion of the preclinical stage, human trials can be applied for (clinical research), initially on healthy volunteers (Phase I) in order to answer additional safety questions and for dose-finding, subsequently on the actual target population in order to prove preventive or therapeutic efficacy and safety (Phase II and III). If these phases have been concluded successfully, market authorisation can be requested. However, safety and efficacy under real-life conditions continues to be monitored (Phase IV).

By far not all initially promising product candidates can be developed into safe and effective medicines or medical devices. The success criteria (safety, efficacy, cost-effectiveness) are continuously tested and only the most promising candidates selected for further development. This also implies that the development of numerous product candidates is terminated over the course of the innovation process. Any product development is thus associated with a considerable risk of failure.

R&D activities up to and including Phase I clinical studies can be conducted wherever laboratories and hospitals with the necessary professional staff are available and where healthy volunteers can be found who agree to act as probands. In industrial countries, clinical studies follow a set pattern of formal approval and procedural steps. A legal entity (normally the manufacturer) bears the costs and overall responsibility for conducting the clinical study and is liable for all consequences. Both a regulatory authority and an independent ethics

committee have to give their approval. All trials with humans have to be entered in registers.

According to given standards, at least the clinical trials with patients (from Phase II) must be carried out in regions where the respective diseases occur – in case of poverty-related and neglected diseases countries of the Global South. In these countries, clinical centres for the conduct of clinical trials as well as governance structures (regulatory authorities, ethics committees, study registers) have to be established or expanded – a great challenge, also because trained professionals often emigrate to the countries of the Global North. For the conduct of clinical trials networks and alliances are currently being developed especially in Sub-Saharan Africa (e.g. Malaria Clinical Trials Alliance, African Vaccine Regulatory Forum, Pan African Clinical Trials Registry) with the aim of establishing and operating sustainably similar structures as in the countries of the Global North.

R&D activities in relation to poverty-related and neglected diseases often require increased resources and time. In many cases, there is still a need for fundamental development work to be put into place so that approval processes take longer and trials are not conducted with as much routine as in the countries of the Global North. These challenges have by now resulted in a stronger cooperative approach. The regulatory authorities in the US (Food and Drug Administration [FDA]) and the EU (European Medicines Agency [EMA]) have increased their cooperation with the WHO, with public and private R&D actors as well as with international funds and alliances in order to coordinate the necessary steps for carrying out clinical trials in accordance with the standards of industrial countries. Research institutions and regulatory authorities of the industrial countries can give considerable support to local institutions in the evaluation of trial data and the assessment of results. FDA and EMA have established special procedures for the fast and cost-efficient assessment of medicines, to some extent also for the market approval in regard to poverty-related and neglected diseases. At present, these procedures have only been activated in a very small number of cases. If more assessments of medicines and medical device are to be performed in the medium term, the necessary resources will have to be increased. The long-term objective is to aim for national/regional autonomy of the countries of the Global South in matters of approval and assessment – a classic task of development, not of research cooperation.

R&D expenditure using the example of one vaccine candidate

Mosquirix[®], the most promising malaria vaccine candidate to date, resulted from a 30-year cooperation between public and private R&D actors together

with the long-term participation of a PDP. The latter provided particular support to the conduct of the necessary clinical trials in Sub-Saharan Africa. In 2008 the conception of the clinical trial for the proof of efficacy began. From 2009 onwards 15.500 babies and infants in eleven clinical centres in Sub-Saharan Africa received four vaccinations each and were subsequently monitored until 2014. Most African centres received scientific support from European or US R&D institutions. It became apparent that even with a considerable vaccination effort, malaria can only be partially prevented (approximately one-third fewer cases). On the basis of the approval application numbering 250,000 pages, the EMA issued a positive risk-benefit assessment in 2015, but it is unclear whether the schedule of four vaccinations within 18 months can be implemented under real-life conditions. The WHO has demanded additional pilot projects with approx. 1 million participants. A recommendation could only be given following the evaluation of these pilot projects. According to the manufacturer's own information, the company has invested more than 600 million US-Dollar to date, the PDP an additional 200 million US-Dollar (mainly donations by the Gates Foundation). No figure has been given for the costs of scientific support provided by European and US institutions. It is not clear at present how the stipulated pilot projects are to be financed. For the pilot project the manufacturer estimates costs of 20 million US-Dollar only for the necessary vaccine production (5 US-Dollar per vaccination dose).

Opening up of research infrastructures and cooperative use (Open Innovation)

3.2

Medical basic research as well as substance discovery and development these days involve the use of expensive high-tech equipment (including maximum-resolution microscopes, DNA sequencing technology, high-throughput screening technology, comprehensive substance repositories, including powerful data processing and storage technology). These research infrastructures are currently being established and expanded with considerable resource input, predominantly in industrial countries as well as in some newly industrialized countries. In Europe, they are increasingly interconnected and used jointly. Opening up and using these facilities also for research into neglected diseases are key elements in improving the current situation, because at present establishing comparable infrastructures in developing countries seems almost impossible. The international research networks and open data exchange platforms currently being established as part of the malaria genome research – such as the Plasmodium Diversity Network Africa (researching genetic diversity and biomarkers for the

emerging parasite resistance to artemisinin in Sub-Saharan Africa) or the Genomic Epidemiology Network (mapping the genome variance of the most widely spread plasmodium species) – could lead the way for research activities also in other diseases. They all make their research data and results freely available online.

Many companies, too, are starting to open up their R&D infrastructure to the development of medicines for poverty-related and neglected diseases. This opening can take different forms, therewith giving rise to a wide range of interpretations of what is to be understood and subsumed under the term Open Innovation. The currently probably most extensive experiment was initiated in 2010 by the UK pharmaceutical company GlaxoSmithKline with the aim of testing the extent to which the business model of open-source software development, i.e. the cooperation of volunteers creating products that do not belong to one company alone, could be transferred to the development of medicines. Its central elements are a patent pool and an open lab. The patent pool includes the intellectual property rights to malaria-specific lead compounds discovered in-house by the company with the associated data and information. They are freely accessible and usable for the development of medicine in the fight against poverty-related and neglected diseases (except HIV/Aids), on the condition that developing countries are subsequently guaranteed an equitable access to the products. This patent pool has attracted a great response in only a few years. More than 40 public and private R&D actors are involved (but no Germans as yet). In the meantime, it has been handed over to the World Intellectual Property Organisation (WIPO) which runs it in conjunction with an US non-profit organisation. In the open lab, external scientist can use the company's R&D infrastructures for activities relating to poverty-related and neglected diseases on the condition that they agree to a subsequent equitable access to the products. This initiative is now also supported by the European Commission, which co-finances research activities over several years by experienced scientists in the open lab.

It is impossible at present to come up with a realistic estimate of the extent to which different forms of Open Innovation can sustainably and significantly boost R&D activities in relation to poverty-related and neglected diseases. Even if open infrastructures can reduce the current obstacles regarding R&D in PRND and open up good opportunities for participation and utilisation, they are not automatically free of charge. The mandatory (pre)clinical trials up to product authorisation become more extensive, expensive and carry greater responsibility with every phase. Only if the necessary funding for the entire innovation process can be provided, will a contribution towards the fighting of these diseases arise from this.

Market-based funding mechanisms and neglected diseases

4.

In industrial countries, even large-scale medical product developments are to a significant extent funded by the market. The main burden of the R&D tasks associated with considerable risks is borne by the producers of new medicines, but in return they are granted intellectual property rights, guaranteeing them exclusive commercial use of the outcomes for a limited period of time, thus enabling a return on R&D investments. Rights to commercial use can be traded through licenses. In industrial countries, this approach permitted the commercialisation of numerous R&D activities and thus the refinancing of associated costs through subsequent product prices. In this model, public budgets co-financing the respective national healthcare system are not burdened with the costs of product development, but with those of reimbursement for the use of the resulting medicines for which the initially sole manufacturer can determine the price. Of particular relevance in the medical innovation system are temporary property rights for the commercial use of

- > *inventions* – these are mainly protected through patents (substances, production processes, formulations and application indications can be protected by patent law) – as well as
- > *data and results from clinical trials as well as approval documents* – these are protected by procedures established in pharmaceutical law regarding data exclusivity and document protection.

For as long as their exclusive commercial use is guaranteed, manufacturers enjoy considerable leeway in setting a price that permits positive returns on investment (profits) through the (re)financing of R&D expenditure. After the end of this protection period, other manufacturers can bring out equivalent products (generics) at reduced expenditure, because important product information (formulations, areas of application) are openly accessible and full references can be made to the original with regard to safety and efficacy and also monitoring and conditions of use. As only biological equivalence to the original has to be proven, development and approval costs remain comparatively low. The subsequent competition between manufacturers overall results in considerable price reductions. The price level of the respective substances is then largely determined by production costs and profit margins of the generics manufacturers.

This basic structure of a commercialised pharmacological innovation process has given rise to different strategies and market dynamics: Large research-based pharmaceutical companies, in particular, develop so-called product port-

folios that contain several product candidates at all stages of R&D as well as approved medicines. R&D activities, risks and costs are pooled within the company and pay-as-you-go financed from the income from approved products. Even if the funding structures are known in principle, individual R&D expenditures remain highly non-transparent to outsiders (this applies also, but not exclusively, to commercial institutions). Furthermore, the time-limited refinancing options provide manufacturers with an argument for justifying ever higher market entry prices for new medicines. Intellectual property rights established in the industrial countries permit patents to be linked to other protective rights, thus making it possible to continuously extend the time limitation of the manufacturer's monopoly. The resulting higher profits represent a considerable incentive for R&D and attract investments. By contrast, areas of medicine where such profits cannot be achieved are neglected in research – even in industrial countries. Examples for this are rare diseases or antibiotics. However, taking intellectual property rights as the sole reason for R&D neglect falls short, because the same neglect also occurs in medical processes in which the described protective rights are entirely absent (e.g. for non-product-related innovations, care processes).

The governments of numerous industrial countries attempt to support health areas of R&D neglected in their own national territory through diverse measures, such as increased public funding for research, fee reductions in assessment and approval procedures, tax credits or innovation funds. Some of these measures could also promote R&D activities on poverty-related and neglected diseases. Some are already established (for example, in recent years many industrial countries have expanded their support of research on these diseases). Others are the subject of controversial debate (e.g. tax credits or R&D funds). Their contribution is that at least some part of R&D costs does not have to be refinanced through product prices and/or that additional incentives for R&D are provided.

Protection of intellectual property – the international situation **5.**

For decades, the advantages and disadvantages of the time-limited protection of intellectual property as an instrument of economic political control have been the topic of controversial debate. On the one hand, it may attract considerable R&D investments that are an essential requirement particularly in the pharmaceutical industry. On the other hand, within the context of poverty-related and neglected diseases, these same protection mechanisms are blamed for both the R&D problem (diseases that particularly affect developing countries are neglect-

ed by R&D) and the access problem (available medicines are often prohibitively expensive for poor countries). Advocates and opponents of protective mechanisms agree that there is an international conflict of interest between safeguarding R&D investments and the access to medicines in developing and newly industrialized countries. In consequence, the special configuration of national law and its international harmonisation play a very important role in the balancing of interests and mediation in this conflict.

Granting and safeguarding intellectual property rights are concerns of the national state, as the protection basically only applies in the country in which it has been granted. For patents, though, there have long been efforts towards an international harmonisation. In this context the activities of the WIPO (a UN sub-organisation) as well as those of the independent World Trade Organization (WTO) are of particular relevance.

The situation until the 1990s

5.1

In the 1970s, some internationally negotiated treaties administered by the WIPO harmonised patent registration procedures. Member states committed amongst other things to treat national and foreign inventors equally and established relevant authorities and accepted WIPO-international application procedures of patent pre-registration. However, it remained up to individual countries to decide for which technology sectors under which conditions and for which periods of time they would grant exclusive rights. In this context, a wide interpretation of the concept of technology, the patentability of even minor innovations and long protective periods are described as high level protection (prevalent in industrial countries) and the restriction to individual sectors, a stipulation of a high degree of innovation and short protective periods as low level protection (tends to apply more to newly industrialized countries). Despite centralised patent registration procedures, differences in national regulations thus still made it possible for patents granted in one country to be rejected in another.

Some newly industrialized countries made strategic use of this situation, particularly in the area of pharmaceuticals, in order to deal with the access problem; from the 1970s onwards, this was particularly prevalent in India: patents were only granted for short periods of time for technical procedures, but medicines were excluded from patenting. In combination with simplified national approval procedures for medicines and market protection measures, this gave rise to a pharmaceutical industry specialised in the circumvention of procedural patents and the immediate generic production of new brand-name product without the need for costly pharmacological R&D of their own. Many develop-

ing and newly industrialized countries attach higher value to the human right to health, one of whose requirements is an affordable access to medicines, than to the ever expanding protection of intellectual property rights and refinancing of R&D investments of foreign corporations, promoted through the establishment of so-called patent thickets. Particularly, because their products were not specifically intended for the markets of developing and newly industrialized countries and the contributions to R&D refinancing thus pure windfall gains for the patent holders.

As an agreement between industrial and newly industrialized countries within the WIPO was quite unlikely because of the comparatively strong position of the developing and newly industrialized countries, the industrial countries were looking for a body outside of the WIPO in order to assert their interests in relation to innovation protection. They found it in the world trade negotiations.

The situation since the turn of the millennium

5.2

Within the framework of the world trade negotiations, the industrial countries succeeded in the 1990s to link the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) to trade agreements. The central TRIPS regulations are:

- > Patent protection is granted for inventions in all areas of technology (national refusal of patents e.g. for active pharmaceutical ingredients no longer an option).
- > The minimum patent term is 20 years from filing the application.
- > Disputes are settled within the WTO trade regime (WTO panels with wide-ranging options of imposing sanctions even against states).
- > In case of national emergencies, the procedures can be limited through so-called flexibilities.
- > Technical support is granted to developing and newly industrialized countries regarding the implementation of the treaty together with long transitional periods.

This agreement, acceptance of which is an automatic prerequisite to WTO membership, increasingly ruled out the patent circumvention strategies used by individual newly industrialized countries for the protection of their population's health. On the one hand, it leads to a global strengthening of R&D investment protection. On the other, it is supposed to mediate between this protection of investments and the supply of medicines in case of national emergencies. The particular purpose of the flexibilities is to limit the significantly exacerbated

problem of accessibility. They had already been included in the TRIPS agreement and were confirmed and specified in the Doha Declaration. The flexibilities continue to provide a certain leeway in determining the level of protection; they permit compulsory licensing of ongoing patents in case of national health crises.

Industrial countries, foremost the USA, are at times ascribed ambitions to further increase existing protection standards. Critics take the view that these ambitions are likely to fail in international negotiations due to the resistance of newly industrialized and developing countries and that the industrial countries are therefore trying to raise these standards within the framework of bilateral trade agreements. As EU member states have transferred numerous tasks of the common trade policy to the European Commission, this report has examined potentially relevant EU trade agreements in this respect. The analysis provided no evidence of EU trade treaties systematically curtailing the degree of freedom given to national governments under the TRIPS agreement. As a rule, these treaties are worded so broadly and at time so ambivalently as to offer a wide scope for implementation that can be used equally in the interest of the patent holders and for the purposes of health and development policy concerns.

TRIPS and other trade agreements can regulate trade-related aspects of intellectual property rights. However, such regulation presupposes that the respective products have already been developed and are thus tradeable. This means that in national health crises these treaties and the agreed flexibilities are used to cope with the problem of access to available products in developing and newly industrialized countries. There are different assessments as to how well this works out.

Insufficient research incentives particularly on diseases that occur almost exclusively in developing and newly industrialized countries (R&D problem) cannot be compensated by trade agreements alone. This is because trade agreements regulate market mechanisms which per definition fail with regard to poverty-related and neglected diseases. In cases of financially weak demand (i.e. when product prices cannot sufficiently refinance R&D costs and no profits can be expected), the funding model based on intellectual property rights does at least not function sufficiently. The less favourable the ratio of required R&D expenditure and (re)financing options by way of product sales, the greater the importance of such supplementary or alternative funding mechanisms that uncouple R&D costs or rather their refinancing from product prices.

Government measures to boost research and development

6.

In recent years, some countries have increased their national commitment to boosting R&D on poverty-related and neglected diseases (PRND R&D). A comparison of governmental commitment in Germany on the one hand and the UK and the US on the other – two countries of equal importance as sites of medical R&D – clearly shows that both the UK and the US governments have attached far greater importance to the support of PRND R&D and that in both countries there seems to be a mutual effect of reinforcement between public commitment on the one hand and philanthropic as well as commercial commitment on the other. All three countries use the following long-established governmental instruments:

- *promotion of national research* to strengthen basic research and early product development especially in their own country;
- participation in the *European and Developing Countries Clinical Trials Partnership* (EDCTP), a cooperation program almost exclusively implemented through public R&D institutions with the aim of expanding capacities for conducting clinical studies in African countries in compliance with international standards (the US is not officially involved in the programme, but US R&D institutions participate in individual projects);
- promotion of internationally acting non-profit *product development partnerships* explicitly for the support of product development in cooperation with public R&D establishments and industry;
- promotion of *R&D structures in developing countries*.

However, on a case-by-case basis, both the US and the UK employ these instruments for R&D promotion on a much greater scale than Germany. In Germany, the 2011 concept by the Federal Ministry of Education and Research (BMBF) for the promotion of poverty-related and neglected diseases initially mainly reorganised and reframed instruments that had already been established for many years; it was only the continuation of the concept in 2015 that envisaged a financial expansion for some of these instruments. Since then, the corresponding national research promotion is to be directed to a much greater degree by the German Centre for Infection Research (Deutsches Zentrum für Infektionsforschung [DZIF]), a new network of long established R&D facilities. To which extent there is a more explicit focus on the specific problems of developing countries than in earlier structures remains an open question. As in many other industrial countries, PDP promotion had originally been assigned to the

department of economic cooperation and development. In 2011, instead of the required increase in funding, PDP promotion was switched to another department. This was justified by pointing to the need to first gain experiences and evaluate instruments. From 2016 onwards, even a doubling in funding (10 million Euro per annum for PDP promotion in total) does not yet even equate to one-sixth of the UK PDP support.

As part of US and UK research support, Open Innovation elements, primarily open access to research results, are furthermore pursued with much greater political commitment than in Germany. These make it easier for other R&D actors to utilize and further expand existing bodies of knowledge. In addition, both the UK and the US governments are testing further measures in order to incentivise and reward commercial R&D commitment in particular. To that end, the UK government relies on tax credits and comprehensive guaranteed purchases of newly developed products, the US government on vouchers by state authorities for the prioritised and lower-cost processing of applications and on the support of specific funds (different concepts for funds and their current implementation status are presented in the report).

No internationally agreed approach towards a boosting of R&D activities is currently apparent, neither in the generation of new funding sources nor in the handling and administration of existing support structures. There are as yet no international research funds with the explicit objective of providing a significant amount of funding for medical R&D on poverty-related and neglected diseases – despite the continuously repeated demands since the turn of the millennium, mainly channelled through the WHO. Even within the EDCTP, the only achievement so far has been the coordination of participants' R&D activities, but not a joint administration of financial contributions from European member states together with contributions by the European Commission.

The stated measures to tackle the R&D problem mostly start from the patent-based medical innovation system without fundamentally calling it into question or wanting to overcome it. Continuing attempts to address the associated access problem to new medicines and medical devices rely on further multilateral initiatives for a socially sustainable access to products.

Initiatives on equitable access to products

7.

Since the turn of the millennium, various bi- and multilateral initiatives have been started with the purpose of making medicines and medical devices available for fighting poverty-related and neglected diseases in developing and newly industrialized countries:

- The global vaccine alliance Gavi pools the vaccine demand of currently 54 developing countries, purchases vaccines in bulk and provides manufacturers with guaranteed sales over several years. Thanks to financial support from industrial countries and philanthropic foundations, the vaccines can additionally be subsidised (the 20 poorest countries are given them free of charge; in line with their increasing economic power, participating countries have to bear an increasing share of the costs themselves).
- The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) provides relevant medicines and medical devices for developing and newly industrialized countries (programmes in more than 100 countries). Here, too, the required products are subsidised for the poorest countries through financial support from industrial countries and philanthropic foundations and participating developing and newly industrialized countries have to bear an increasing share of the costs themselves in line with their increasing economic power.
- The Global Financing Facility Trust Fund (GFF Trust Fund) was started in 2015 to accelerate advancements in the health of women and children; it also aims to improve access to medicines and medical care and to close specific R&D gaps (treatments suitable for children). The initiative is currently being tested in four African pilot countries.

The aim of these initiatives is to improve the supply of medicines and medical devices to the health systems particularly of the poorest countries. At the same time, the programmes divide the global market for these products into a non-commercial and a commercial sector. In the non-commercial sector, the aim is to keep product prices as low as possible. The poorest countries, in particular, are exempted from the (re)financing of R&D costs (via product prices) and in some instances, they receive additional subsidies so that they also do not have to bear the full production costs. With increasing economic power, countries are expected to bear a great share of the costs also in this non-commercial sector. However, positive returns on R&D investments are only to be envisaged for the commercial sector (total demand from industrial countries and private demand from developing and newly industrialized countries).

Such differentiations which mainly unburden countries with weak economic power from contributing to the (re)financing of the required R&D costs are roughly described as a socially sustainable product access, however with a wide range of interpretations as to this social sustainability. This report also introduces an initiative that aims to anchor a socially sustainable product access already at the start of the innovation process in the out-licensing of patents (socially sustainable licenses).

The primary aim of these initiatives is to counter the access problem in relation to poverty-related and neglected diseases. It remains to be seen to what ex-

tent the boosting of demand will counteract the failing market mechanisms in relation to poverty-related and neglected diseases and thus provide indirect incentives for dealing with the R&D problem.

Location Germany: Actors, research areas, strengths 8.

Germany possesses highly competent public and private institutions that in their totality cover almost the entire spectrum of R&D on poverty-related and neglected diseases, even if most activities are related to the “Big Three”. These R&D institutions are active in all product areas (medicines and medical products) and all stages of R&D (basic research, preclinical research, clinical trials), with some focal points and particular strengths apparent:

- The commitment to fighting tuberculosis is outstanding due to its variety and its results. Activities aiming for the further development of different diagnostic techniques also stand out.
- German actors also demonstrate a special expertise and creative new approaches in the early R&D stages of vaccine development. By comparison, the wealth of creative ideas in the development of new medicines lags behind.
- German companies have further particular strengths in the battle against disease-spreading insects, even though this is currently rather seen as a niche area. As the habitats of these insect also spread into the northern hemisphere in the wake of climate change, in the future this area is likely to become more important in industrial countries, too.

For activities in the fight against poverty-related and neglected diseases, German R&D establishments not only make use of national support instruments. Yet it is very difficult (and at times impossible) to identify PRND-related activities in the respective national funding data bases, because no separate PRND project lists or specific search criteria have been recorded and the selection has to be made on the basis of case-by-case review of project descriptions. Thus it is not clear to what extent the potentials of various national innovation incentives such as KMU-innovativ or BioÖkonomie 2030 have been fully exploited in terms of poverty-related and neglected diseases. In addition to national funding options, German R&D establishments also use the opportunities provided by European framework programmes for research and innovation including the special structures of EDCTP and Innovative Medicines Initiative (IMI). Some actors are also involved in transatlantic projects and international contests of ideas, in which they achieved some outstanding results.

This snap-shot of German R&D activities did not find any evidence that the patent-based innovation system is being overcome. Procedures for the protection of intellectual property are used intensively, but German R&D actors are not yet involved in the joint use of patents in patent pools. In the implementation of other Open Innovation options, too, German R&D actors to date are anything but trailblazers. There is thus no indication of a solution to the fundamental problem of access to new medicines and medical devices in developing and newly industrialized countries associated with protection mechanisms. For that reason, the initiatives aiming for a socially responsible access to medical products continue to be of great relevance.

Areas of activity

9.

At present, the German Federal Government sees the main responsibility for boosting PRND R&D within the remit of the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung [BMBF]) that at present coordinates its health-related activities mainly with the Federal Ministry of Health (Bundesministerium für Gesundheit [BMG]) and the Federal Ministry for Economic Cooperation and Development (Bundesministerium für wirtschaftliche Zusammenarbeit und Entwicklung [BMZ]). TAB takes the view that the impact of the already established components of the funding concept for poverty-related and neglected diseases could be increased with the addition of further research-policy components and with interlinking these with activities regarding economic, development and health policy and merge them to an overall strategy of the German Federal Government.

Research policy

9.1

With the department-specific PRND funding concept initiated by the BMBF and the department's own Africa strategy, important elements of the direct support for PRND R&D are being pooled. The four components of the funding concept (national research, EDCTP, PDP and research networks in developing countries) not only finance basic research on PRND in Germany, but also strengthen the networking of R&D actors in both north-south and south-south collaborations. These collaborations are important elements in the transfer of knowledge and the establishment of capacities for all R&D activities along the entire medical innovation chain and also in the coordination of R&D activities in order to identify blind spots and avoid duplication. After the establishment phase, regular reports on the progress of this programme are to be generated. As

a specific element of responsible research and innovation (RRI), they are to be included in the future into the comprehensive reports by the Federal Government and the relevant expert commissions on Germany as a research and innovation location.

The four components of the funding concept cover all steps of the medical innovation process. But the amount of funding is still far too small particularly for conducting clinical trials in the course of product development, even after the increase. It seems almost impossible that the envisaged funding budgets will allow for rapid advances product development. The potentials of non-profit PDP with the aim of developing products against PRND cannot be fully exploited in this manner. A strengthening of early R&D measures to some extent comes to nothing if later approval-relevant clinical trials are delayed for budgetary reasons or if they have to be stretched over long periods of time.

Other research-policy measures should accompany the BMBF programme. These include first and foremost the opening of or rather access to research infrastructures, data and results or also the joint use of patents in patent pools for R&D on PRND. With regard to modern high-tech research infrastructures (substance libraries and biobanks, laboratory automation, supercomputers), established in Europe with considerable public support and in any case increasingly used on a joint basis, special procedures for PRND R&D should be established (e.g. low-cost or free access and fields of use, specific contracts) in order to make this high technology usable for R&D on PRND in the best possible way. For publicly financed innovation initiatives – from KMU-innovativ and BioÖkonomie 2030 to the European Innovative Medicines Initiative (IMI) – it should also be assessed to what extent they could enable specific R&D on PRND. Another important step would be the opening up of PRND-related national and/or European calls for proposals also to research institutions in the Global South.

Interlinking with remits in development cooperation

9.2

A significant part of the necessary R&D activities, at latest starting at the proof-of-concept stage, can only be carried out in countries where the respective diseases are endemic. For this reason, the required clinical centres and also supervisory authorities have to be established and expanded both on a national and on a transnational basis. As, besides their research tasks, these clinics also have responsibilities regarding medical care, measures of BMBF and BMZ should be coordinated and interlinked so that they complement each other as good as possible.

Even if R&D costs for poverty-related and neglected diseases can be successfully uncoupled from product prices for at least the least developed countries, there are still production and distribution costs to consider that will exceed the financial capacities of the affected countries in view of their inadequate social security system. Bilateral measures within the framework of health related development aid together with multilateral alliances and funds help to improve a socially sustainable access to quality-tested medicines and medicinal devices in developing and newly industrialized countries. The health-related effects of these initiatives (including Gavi, GFATM) could be enhanced if the currently highly diverse geopolitical coverage could be successfully standardised and expanded as well as the respective activity ranges and budgets increased. As financing the initiatives on socially sustainable product access falls under the remit of the BMZ, a cross-departmental coordination between BMZ and BMBF is obviously required.

Interlinking with measures of economic and innovation policies

9.3

Some industrial countries attempt to boost weak market mechanisms in the medicines and medical device sector with the help of economic policy measures. These include tax credits for R&D measures, rewards for PRND R&D with vouchers or the massive boosting and securing of product demand. In Germany, too, a debate could be triggered as to whether economic policy measures with the aim of specifically strengthening commercial commitment to PRND R&D could be coupled with procedures that safeguard an equitable access to products.

In parallel with the PRND funding concept by the BMBF, the then Federal Ministry of Economy and Technology (Bundesministerium für Wirtschaft und Technologie [BMWFi]) set up a health-economy export initiative in 2011 in order to support German companies in the development of new sales markets and to establish Germany as one of the leading exporters of health products and services. As the BMWFi takes the view that not all options have yet been exhausted particularly in the countries of Sub-Saharan Africa, a closer interlinking of measures with those relating to development and economic cooperation could be helpful, thus permitting the development of synergies between diverse activities (provided that this would not restrict any TRIPS flexibilities).

International health-policy and procedural areas of responsibility**9.4**

Procedures established by the regulatory authorities in the industrial countries and by the WHO regarding centralised benefit and risk assessment currently constitute important elements in making medicines or medical devices accessible to the respective entitled countries via multilateral initiatives. They bridge incomplete capacities, particularly in Sub-Saharan Africa. If new substances are to be advanced to approval in increased numbers, the resulting increased assessment expenditure has to be covered. In parallel, there is a need to establish and expand structures of national and regional governance within the Global South in order to decrease the corresponding dependence on institutions in the industrial countries. The EDCTP European-African initiative already takes on important training tasks with regard to the medical-ethical assessment of clinical trials. However, this is only one aspect in the evaluation of medicines and medical devices. Establishing the necessary governance structures cannot be achieved by research collaboration alone, but requires development cooperation and international commitment to health policies. Here, too, there is a need to coordinate and interlink activities.

On a case-by-case basis, it could be tested by how much the time and personnel requirements for the proof of efficacy and safety of medicines against poverty-related and neglected diseases could be reduced if the methodology of study designs was adapted. In industrial countries, this is often possible for very rare diseases (e.g. a provisional early approval after the successful conclusion of Phase II, lowering the requirements on statistical tests). However, this is regularly linked to an intensive monitoring of the application of the respective substance under real-life conditions – a particular challenge for developing countries whose monitoring capacities in this respect are limited. It would be necessary to find and establish a form of safety monitoring that is practicable under the respective local conditions.

Another aim should be to improve PRND documentation (epidemiological register as well as documentation of R&D activities and their funding). In some instances, a greater level of harmonisation is required in determining disease-specific R&D requirements and coordinating the corresponding tasks and activities. This coordination increasingly takes place through global disease-related initiatives (e.g. Stop TB Partnership, Roll Back Malaria Partnership), European research collaboration projects (currently financed through Horizon 2020) as well as globally active PDPs with their specific product pipelines. It is at present impossible to assess conclusively whether further centralisation and global control could achieve greater successes in product development.

Instead of global solutions, recent years have seen a rise in numerous attempts at small-scale solutions ranging from product supply programmes to patent pools. Even if views differ as to the extent that these individual components can contribute towards a sustainable improvement of the situation, some trends become clear in this debate: It is generally agreed that the least developed countries must be most comprehensively supported with regard to access to medicines and medical devices. These countries are generally not expected to contribute towards the necessary R&D costs; for the supply to these countries, production licenses for individual medicines are granted free of charge. Additional subsidies may in some cases even permit products to be supplied entirely free of charge. The majority accept that industrial countries finance the existing medical innovation system to a large degree through product prices. From countries with economies somewhere in between these two extremes, the industrial countries, at least, demand and call for a contribution towards the costs of R&D. In most cases, bilateral agreements are in place. There is still a wealth of opportunities here, not least because many processes are of only limited transparency. A greater level of transparency and harmonisation of procedures in determining the price of new medicines and medical devices should be aimed for. The necessary debate about fair R&D funding and fair prices of medicines should be sought at an international level. While it is likely to provide only a limited solution to the problem of R&D on poverty-related and neglected diseases, it may be helpful to reduce the problem of access to medicines for diseases that occur in industrial as well as in developing and newly industrialized countries.

Combining department-specific measures to an overall strategy by the Federal Government and boosting its funding 9.5

Poverty-related and neglected diseases are associated with problem areas and challenges that come under the remit of various government departments (research, product development, economic development up to questions of international trade including protection mechanisms for R&D investments, development cooperation, global health policy). A funding concept as a research policy instrument had been a necessary and important first step to face up to the current global problem caused by poverty-related and neglected diseases. However, combatting this problem successfully requires more than department-specific commitments. The next step should be a coordinated approach by several departments – an overall strategy by the Federal Government with specific and accountable measures for its implementation. These measures should be the subject of regular reports.

The Office of Technology Assessment at the German Bundestag (TAB) is an independent scientific institution which advises the German Bundestag and its committees on questions of scientific and technological change. TAB has been operated by the Institute for Technology Assessment and Systems Analysis (ITAS) of the Karlsruhe Institute of Technology (KIT) since 1990. It has been cooperating with the Helmholtz Centre for Environmental Research – UFZ, the IZT – Institute for Futures Studies and Technology Assessment and VDI/VDE Innovation + Technik GmbH since September 2013. The Committee for Education, Research and Technology Assessment of the German Bundestag decides on TAB's work programme, which also includes subjects proposed by other parliamentary committees.



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