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Science and Technology Options Assessment

S T O A

Extending the pipeline – toward a comprehensive and coordinated EU approach to Poverty Related Diseases

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Study

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Executive Summary

For many diseases, medicines and health care systems are badly needed but not yet developed. Despite ambitious initiatives by governments, international organizations and companies, their treatment suffers from underinvestment, underproduction and uneven distribution of medicines. This situation is often referred to as the '*pharmaceutical gap'*. Diseases fall into such pharmaceutical gaps when they are important for public health, but lack effective pharmaceutical treatments because of insufficient scientific knowledge or because of market failure. The European Union has taken a role in meeting these pharmaceutical gaps by investing in drugs research and development for poverty related diseases such as HIV/AIDS, malaria and tuberculosis and some other neglected infectious diseases with a high burden of annual deaths.

How effective are Europe's efforts to diminish these pharmaceutical gaps? The objective of this report is to supply policy makers and parliamentarians of the European Union with a set of policy recommendations concerning the EU strategy on global human health and health care strategies, with a particular focus on EU strategy in the fight against PRDs. These recommendations should ground in a thorough analysis of the assumptions and bottlenecks in the current situation. The main question of this study therefore is how, given the complexity of the issue, the EU can make a meaningful contribution to closure of pharmaceutical gaps and ultimately to the enhancement of universal health?

To examine assumptions and bottlenecks of current EU policies we first introduce a theoretical framework built on two models (chapter 1 and 2):

1) the model of the *Extended Pipeline, which widens* the scope of the traditional drug-development pipeline conventionally used in the pharmaceutical industry. The Extended Pipeline takes the delivery and the (social) impact of the drugs into account too. This perspective enables decision-makers to take evidence-based considerations into account right from the start of the drug development process.

2) the *Social Determinants of Health model* (SDM). The SDM shows clearly the connections and relationships between health and its social determinants. Access to drinkable water; sanitation; nutrition; comfortable houses; work conditions; education; gender disparities; social cohesion; lifestyles are all determinant, for different degrees, of our biological health.

Taken together, the theoretical framework combines a "science-based" analysis of the steps involved in the pipeline with the empirical findings and data of epidemiology, economics and sociology. From this perspective, it appears that most successful actions against PRDs as malaria, HIV/AIDS and tuberculosis are the result of an integrated approach based on the involvement of African countries in synergy with input from EU and other agencies (chapter 3).

However, at least four types of gaps appear in the fight against PRDs when we confront the results of the theoretical framework with current EU policy initiatives:

1) the Science/Society Gap (the distance between scientific and technological improvements and their effects in real life)
2) the Policy/Reality Gap (how to overcome the market failure of pharmaceuticals for PRDs);
3) the Euro/African Research Gap (the need for involvement of African scientists in prioritization and R&D of new drugs);

4) and finally the Central Planning/Local Implementation Gap (how to translate good plans in actions).

Given these gaps, what are the main issues that should be addressed in European Union policy? In *chapter 4* we select several issues, categorized along the axes of the extended pipeline. The first group of issues concerns matters of *design*. The second group of questions concerns matters of *coordination*. All these topics, it is shown, call for a flexible integration. These issues were discussed in an expert meeting organised by the Rathenau Institute in April 2008.

Combining the four gaps selected in chapter 3, the design and coordination issues suggested in chapter 4 and the deliberations in the experts meeting we conclude with 9 recommendations.

1. *Abridge the Science/Society gap*. Science-based innovation needs to be informed by the social contexts in which its products will be used. Instruments to abridge the gap include closer collaboration with TDR and extensive consultation of the UN commission on social determinants, the EDCTP and TDR.
2. *Change focus and priorities of the EU's PRD policy:* PRDs cannot be addressed exclusively by developing and supplying drugs. The EU should pay more attention to healthcare infrastructures and prevention of diseases.
3. *The role of developing countries in the extended drug delivery pipeline needs to be enhanced*, since joint planning and prioritization of the research agenda by all stakeholders is essential to ensure better coordination and focus in clinical trials. Furthermore, EU –African projects should have African scientists as their principal investigators.
4. *Intensify EU participation in partnerships with the pharmaceutical industry*. Tailor-made partnerships all along the extdend pipeline are generally acknowledged to be a prerequisite for successful drug delivery.
5. *Clearly define guidelines for EU policy making on PRD in the 7th and 8th framework programme.* At the moment, clear guidelines are lacking. The EU needs to formulate a new and coherent Strategic Program for Action and keep it up to date in an ngoping learning process.
6. *Implement a strong health support structure as a base for the Programme for Action*. An effective strategy must be based on an integrated approach, aimed both at the development of drugs, vaccines and diagnostic tools and at improving health care systems. The organizational support of the Program for Action is currently lacking.
7. *Improve the coordination of EU Directorates-General*. The coordination of the activities of the EU Directorates-General External Aid and Development, Trade and Research still leaves much to be desired . Regular inter-departmental meetings on PRDs are essential if the EU is to achieve its aim of becoming a learning organization.
8. *Improve the evaluation of actions and results.*All global efforts in the fight against PRDs should be periodically monitored and evaluated in two main areas: biomedical activities and activities aimed at improving social and economic conditions.
9. *Take care for a proper balance between the "Big Three" and neglected diseases*. It is often much easier (and less expensive) to treat neglected tropical diseases than the "big three". Interventions against neglected diseases could dramatically improve the standard of living, and would serve both to bring nations closer to the Millennium Development Goals set by the UN.

Medicine is a social science and politics is nothing but medicine writ large.

Rudolf Virchow (Berlin 1847)

Introduction

In November 2004, the WHO published the report *Priority medicines for Europe and the World*. The purpose of the Priority Medicines for Europe and the World project was to study pharmaceutical innovation from a public health perspective. The report's premise is that 'pharmaceutical gaps' should be a thing of the past. Pharmaceutical gaps have been defined as:

> "those diseases of public health importance for which pharmaceutical treatments either do not exist (lack of basic scientific knowledge or market failure) or are inadequate (lack of efficacy or safety concerns or because the delivery mechanism of formulation is not appropriate for a target patient group)" (Kaplan and Laing 2004, p.vi).

The authors of the WHO report identify different types of priority disease subject to pharmaceutical gaps, using evidence-based methodology for estimating the global burden of diseases and predictions of likely health trends. They distinguish between:

- chronic diseases such as ischaemic heart disease,
- acute diseases such as influenza,
- high-burden preventable diseases, such as HIV or alcoholic liver disease,
- high-burden diseases for which no cure exists, such as Alzheimer's,
- high-burden diseases for which inadequate therapies exist, such as cancer and diabetes,
- neglected diseases such as malaria, tuberculosis and "orphan diseases".

The above categories can overlap and are thus not exclusive. However, each type of priority disease poses specific challenges to Europe in terms of allocation of available resources, health care policy, public information, the setting of international research agendas, the building of R&D infrastructure etc.

As part of the STOA/ETAG Global Human Health project, a workshop on *Strategies for the Improvement of Global Human Health* was held on 26 June 2006. The project Global Human Health 2 "Towards effective cooperation on Medicine Research and development" was launched on 1 December 2006 as a follow-up to this workshop. It aimed to:

"contribute to a common European science and technology policy by delivering a basis for decision-making on national and European level to tackle technological gaps in global health and global healthcare strategies".

The first deliverable of this project, 'Assessment of policy practices for stimulating health research', was presented in May 2007. This report focused on two themes related to the development of an EU strategy for bridging 'pharmaceutical gaps'. The first is the emergence of Public-Private Partnerships (PPPs). The second is the attempt to speed up the introduction of new medicines by lowering regulatory barriers. The authors were critical of the idea of 'priority medicines', claiming that this concept is used in too many different settings to be of much analytical value.

The project Global Human Health 2 is a follow-up to this first deliverable. Rather than discussing European action on a wide range of priority medicines, it focuses on Europe's role in combating poverty related diseases (PRDs), in particular AIDS/HIV, malaria and tuberculosis. Since PRDs primarily affect people in developing countries, the battle against them is most strongly dependent on political and public action in first-world countries

The objective of this second deliverable of the Global Human Health 2 project is to supply EU policy makers with a set of policy recommendations concerning the EU strategy for combating PRDs.

The first step towards this end was a desk study of the state of the art in PRD research. Inspection of some recent expert reports and evaluations led to identification of the concept of the extended drug development pipeline as one that could provide a framework for further analysis. This framework is presented in Chapter 1. The framework of the extended pipeline was also used as input for an expert committee that met in Brussels on 10 April 2008. The conclusions of this meeting are given in the *Addendum* to the present report. One main conclusion was that research policy in this field needs to be not only science-oriented but also to focus on the social determinants of health. The implications of these social determinants of health are reviewed in Chapter 2, while Chapter 3 studies current EU initiatives aimed at improving the strategy used to combat PRDs. These are compared to the results of the theoretical framework of chapter 1 and 2. In the comparison, four types of gaps between theory and practice appear in the fight against PRDs .

Given these four gaps, what are the main issues that should be addressed in European Union policy? In *chapter 4* we select several issues, categorized along the axes of the extended pipeline. The first group of issues concerns matters of *design*. The second group of questions concerns matters of *coordination.*

Chapter 5 contains the conclusions and recommendations of this report, which are based not only on the discussion paper of Chapter 1, the Social Determinants model described in Chapter 2 and the report of the expert committee but also on subsequent discussions with a number of experts.

1 Towards a comprehensive and coordinated EU approach to poverty related diseases

Globally, AIDS/HIV, malaria and tuberculosis kill almost 20,000 people every day – mainly in developing countries. Other neglected diseases and diarrhoeal diseases are responsible for a further one and a half million deaths annually worldwide.

Much more research on the mechanism of action of these diseases is needed – but above all, we need to combat them more effectively. The present chapter is devoted to the discussion of the 'extended pipeline' for the production and supply of medicines which, it is argued, could be a key factor in improving performance in the fight against poverty related diseases (PRDs).

The pharmaceutical industry traditionally regards the 'pipeline' as the sequence of steps from R&D up to and including the registration and approval of the drug in question. The concept of the extended pipeline widens this perspective by taking into account the supply and impact of the drugs as well, and encompasses a range of measures from policy proposals to *in situ* action. The extended pipeline concept includes the traditional drug development pipeline but goes further to consider such issues as prioritorization of different types of action and different beneficiaries, the training of local health personnel and the provision of the necessary infrastructure.

1.1 Combating PRDs

In September 2000, world leaders at the United Nations Millennium Summit agreed to a set of time bound and measurable goals and targets for combating poverty, hunger, disease, illiteracy, environmental degradation and discrimination against women, known as the Millennium Development Goals. One of these goals is to reverse the spread of diseases, especially HIV/AIDS, malaria and tuberculosis. These killer diseases weigh heavily on global health. An estimated seven million people die of AIDS/HIV, malaria or tuberculosis annually, accounting for 10% of global mortality. Other neglected infectious diseases, including leishmaniasis and schistosomiasis, are responsible for some 500,000 deaths and millions of disabilities every year. A million people die of diarrhoeal diseases annually. What all these diseases have in common is that they have a disproportionate affect on poor people living in developing countries.

The control of these poverty related diseases (PRDs) is of vital strategic importance to the UN. An intrinsic relationship between poverty and disease continues to exist in developing countries. Poverty creates conditions that favour the spread of infectious diseases and prevents affected populations from obtaining adequate prevention and care. Conversely, infectious diseases predominantly affect poor populations and are themselves a major cause of poverty (TDR 2007 p.4). Breaking this vicious cycle is a challenge to the global community as a whole. This challenge is explicitly taken on in the UN Millennium Development Goals. The EU subscribes to these goals as is apparent from the policies it has formulated in this field.

There are several reasons why the vicious cycle of infectious disease and poverty has proven so difficult to break. One of these is the existence of poverty itself. "As the effected populations are poor, there continues to be little incentive for industry, by itself, to invest in the development of effective intervention tools like drugs or vaccines." (TDR 2007 p.22)

This implies that people in the countries where the diseases in question are endemic will be dependent on public or political action by developed countries, philanthropic funds and NGOs (often in partnership with industry) for the provision of (new) drugs and vaccines. Initiatives by global institutions and Western countries such as the EU are of vital importance in combating these diseases and reaching the Millennium Development Goals.

The European Union acts to help control these diseases, both by coordinating and funding scientific research on substances of medical interest and their development into approved drugs and vaccines, and through development aid (COM 2001, COM 2005). Each of the programmes in this field is subject to regular evaluation. There has however been no coherent overall monitoring of the *combined* EU programmes – their effectiveness, their strengths and weaknesses, and how they complement each other. The Scientific Technology Options Assessment unit of the European Parliament (STOA[1]) has therefore commissioned the Rathenau Institute in The Hague to study the strengths, weaknesses, opportunities and threats to EU policy on PRDs.

1.2 A learning process

Despite EU and other initiatives, those actively engaged in the fight against PRDs do not see any marked improvement in the situation[2]. What makes it so hard to combat these diseases? The present research project starts from the assumption that there is no simple solution to the problem of PRDs. Their complexity and dynamics appear to demand a flexible approach that has all the characteristics of a learning process. The analysis given in this report of the EU programme of action against PRDs as a whole may be seen as a contribution to this ongoing learning process.

There are several reasons why it is important to do this *now*. The 6th Framework Programme has recently been completed. During the past five years, the EU has invested significant amounts of money, knowledge and human resources in the fight against the three major deadly diseases. Lessons learned from the experience of the past five years will make an invaluable contribution to the 7th Framework which is just starting. In addition, a number of evaluations and reports of strategic importance have recently been published, which together shed new light on current strategies in the battle against PRDs. These include the Ten Year Vision and Strategy of WHO/TDR (2007), the *Nature Outlook* on Neglected Diseases (September 2007), the IER report on the EDCTP programme (2007) and Mary Moran's study on the New Landscape of drug development in the struggle against neglected diseases (2005).

One of the most troubling insights gained from these studies is that although the number of parties devoted to the combat of PRDs has increased significantly over the past five years, this has not yet led to any significant improvement in the situation[3]. The challenge is a complex one – take for example the issue of drug resistance. In addition, the increased activity as such creates new challenges to the parties involved. Two themes stand out in the recent literature: firstly, the importance of **coordination** and secondly, the need for **evidence-based prioritorization** when it comes to deciding which measures to take in the fight against PRDs. These two themes are also crucial to the topicality of the European programme of action.

[1] For further information on STOA, please visit http://www.europarl.europa.eu/stoa/about/default_en.htm.
[2] For a critical review, see the *Nature Outlook* on Neglected Diseases, September 2007.
[3] There are however some exceptions. As stated in the TDR report, the disease burden for some PRDs has dramatically declined, leprosy and onchocerciasis (the latter thanks to the use of ivermectin) being the prime examples.

1.3 Deliberation with experts on the extended pipeline

The objective of this research project is to deliver policy recommendations to the European Parliament on global human health and health care strategies, with a particular focus on EU strategy in the fight against PRDs. A useful contribution was made by an expert committee composed of the persons responsible for the implementation of the EU programme of action and a number of relevant experts, who met on 10 April 2008 in Brussels.

The remit of the expert committee was to gain further insight in the extent to which the European Union is geared to draw lessons from current ideas about the social, political, technical and economic obstacles to combating PRDs, and how the EU should ideally respond to these lessons in its future policy.

This requires not only knowledge of the results of all kinds of (EU and non-EU) programmes but also the development of well-based concepts that could be used to analyse and evaluate these results. These concepts are however still largely lacking. One major conclusion reached by the expert committee was that, in the light of lessons learnt during the past years, the concept of the '*drug development pipeline'* conventionally used as a means of visualizing the path from basic research on promising chemical compounds to the approval of drugs and vaccines shows clear inadequacies**.** This concept does not embody any mechanism for incorporating new insights concerning key obstacles into the standard pipeline model, or to facilitate alternative approaches to control of PRDs.

The expert committee believed that a new concept that might be called the 'extended pipeline' could play a major role in resolving the above-mentioned difficulties by providing a framework that would facilitate coordination of activities and the introduction of evidence-based monitoring. The extended pipeline concept includes the traditional drug development pipeline but goes further to consider such issues as prioritorization of different types of action (e.g. preventative vs. curative) and different beneficiaries (e.g. children), the training of local health personnel and the provision of the necessary infrastructure. In brief, the extended pipeline is both *longer*, as it does not terminate with approval of the new drug or vaccine, and *wider* as it also includes the environments the pipeline runs through.

The objective of presenting this concept here, however, is not to convince the reader of its worth but rather to stimulate discussion of those matters identified by the expert committee as essential components of the extended pipeline: *evidence-based prioritorization* and *coordination,* both within the drug development process and beyond the conventional R&D trajectory. Are these in fact necessary ingredients of an optimal EU programme of action on PRDs? And would they, taken together, be sufficient to address the problems that have been so eloquently pointed out in recent publications? To what extent are EU actions on PRDs currently informed by these two factors? And what would be required to bring EU institutions into line with the requirements of the 'extended pipeline' concept?

1.4 Arguments for extending the pipeline

> ***A mother cannot afford to go six times a week, often to different places, to access separate services to immunize her child, treat her son's asthma, ensure she has antiviral drugs for her husband, collect an insecticide-treated bednet, receive family-planning advice and discuss whether her daughter should receive a vaccine against cervical cancer. Yet this scenario will remain the reality for millions of women in the absence of a rational and functional health-care provision (Lob-Levyt 2007, p.171).***

This quotation from Julian Lob-Levyt, head of the Geneva-based Global Alliance for Vaccines and Immunization (GAVI), highlights at least three issues that need to be taken into account when developing a coherent combat strategy against PRDs. Apart from (1) the scientific and technological challenges to be confronted in R&D for new drugs, vaccines, and diagnostic tools, the situation sketched above shows that (2) improvement of the basic healthcare systems in developing countries and (3) coordination of the different programmes executed by different parties are crucial for success in combating PRDs.

1.5 Gaps in the R&D pipeline

As many authors have highlighted, there is an urgent need for (new) drugs, vaccines and diagnostic tools in the battle against PRDs which would be not only clinically effective but also safe, affordable, stable during distribution and storage, easy to administer and (to ensure wide usage) well adapted to local cultures (Hopkins et al. 2007, Van Velzen et al. 2007). However, the production of drugs and vaccines that meet these criteria has met with formidable obstacles.

About half of the drugs being developed to treat neglected diseases fail to meet some of these criteria […] The few drugs available are not widely used, owing to problems with safety, administration, cost and increasing resistance of the infectious agents (Hopkins et al. 2007).

The drug development pipeline is the main model used to visualize the path from laboratory research to the approval of drugs and vaccines is. "As most experimental drugs fail in the development phase, the challenge is to produce a sustainable pipeline of new drugs candidates" (Hopkin et al. 2007, p.166). However, the drug 'pipeline' for these neglected diseases is almost dry (O'Connol 2007, p. 157). The conventional drug development pipeline model starts with the identification of a lead compound and usually ends with a new drug being registered, approved and ready for the market.

In wealthy countries, it is taken for granted that research and development on new drugs and vaccines is the first step towards the manufacture of effective products and their subsequent distribution through carefully regulated channels. However, in developing countries the path from lead compound and drug development via market entry to actual administration to the patient is beset by many obstacles such as inadequacies in healthcare systems, infrastructure, logistics and management systems. In many cases, the drug never reaches the patient (Lob-Levyt 2007). In other words, there are clearly gaps in the pipeline. Bernard Pécoul, executive director of the Drugs for Neglected Diseases Initiative (DNDi), has identified three such gaps. The first is located at the interface between basic and preclinical research. The second is represented by the failure of validated candidate drugs to pass on to the next stage of clinical development. And the third is found at the end of the pipeline where the distribution mechanism breaks down for any of a large number of reasons and drugs do not reach the patients who are in need of them (Pécoul 2004, p.20).

1.6 More than R&D alone

The brief account of the gaps in the pipeline given above shows clearly that the difficulties in delivering healthcare to those who need it most urgently are only partly due to scientific and technological problems. As Peter Singer and many other authors have pointed out, many factors play a role in the uptake of health related biotechnologies in developing countries.

The path from basic scientific discovery to effective therapy is rarely rapid or simple, especially in the developing world. […] The complex issues involved in the development of new technologies cover areas as diverse as science, capacity building, culture, economic analysis, foreign investment and imports, public-private product development partnerships, intellectual property and political policy. The fact that these problems have generally been explored with reference to their impact on in the developed world and in isolation from one another means that the overall picture – especially in the developing world - remains unclear (Singer 2007, p.160).

In other words, the R&D pipeline does not pass through a void, but through a complex environment that actively impinges on the flow of the product and can actually give rise to serious additional gaps in the pipeline. In order to tackle global health problems, we need to pay attention not only to what goes *in* the pipeline, but also to its surroundings.

The third point of concern raised by Lob-Levyt is the growing need for coordination of healthcare distribution activities. The number of parties dedicated to the fight against PRDs has increased significantly of recent years. As a result, today a host of different bodies[4] participate in the fight against PRDs and have combined to create the basis for a new generation of drugs and vaccines. Various coordinated R&D programmes aimed at concerted action for drug discovery exist. Despite this increase in activity and in the number of drugs now entering the pipeline, however, there is still no guarantee that effective drugs will soon reach the patients who are in need of them.

In its recently published *Ten Year Vision* (2007), the WHO/TDR warns of the possible downside of the increased activity. As the authors show, too much effort can actually *threaten* the good cause – for example, if activities are not well coordinated at a global level and/or lack a sound evidence-based underlying rationale. Thus, well-intentioned policies may in the end prove to be ineffective or even counter-effective (Moran 2005, TDR 2007 p.28, Lob-Levyt 2007). Key challenges to the global effort can be found in the fragmentation of effort, limited involvement of the countries where the diseases concerned are endemic and neglect of critical research areas (TDR 2007 p.5). Despite such caveats, Lob-Levyt remains relatively optimistic about the situation:

Frankly it is not complicated. Capacity building and additional funds will be required. Above all, political leadership – both nationally and globally – and agreement on a coordinated and sustained effort are vital (Lob-Levyt 2007 p.170).

In other words, *if* the actions of all the parties involved are coordinated properly, current efforts to fight PRDs are likely to gain in effectiveness.

1.7 Extending the pipeline

In view of the specific constraints under which R&D processes designed to generate new drugs and vaccines for developing countries labour, the conventional drug development pipeline model is of limited relevance. Its shortcomings soon become clear when it is applied to a situation in the developing world. Science-centric models for combating PRDs do not provide an effective basis for timely reflection on the political, economic, infrastructural, technical and cultural obstacles that stand between good intentions and really effective therapies.

[4] These include not only governments, industry and academia, but also charitable foundations such as the Bill & Melinda Gates Foundation and the Rockefeller Foundation[4], NGOs such as MSF, OXFAM and UNICEF, global institutions such as the WHO and the World Bank, academic research centres and pharmaceutical companies. Many of these parties have opted to work together in so-called Drug Development Public-Private Partnerships (commonly abbreviated PDPs or PPPs), such as GFATM and the TB Alliance (Moran 2005, TDR 2007, IFPMA 2007).

The expert committee concluded that the science-centred perspective inherent in the conventional pipeline model has three downsides. Firstly, it does not force decision-makers to consider what type of intervention is most needed locally. Once one has started thinking about the fight against PRDs along the lines indicated by the classical pipeline model, alternative approaches or measures that would complement drugs and vaccines are lost sight of. Secondly, the conventional pipeline model discourages decision-makers from thinking about the conditions that need to be considered when developing the type of intervention required. And thirdly, it fails to reflect the importance of strategic partnerships in the different phases of the drug development and distribution process from policy makers via laboratories to patients.

In the opinion of the expert committee, the conventional development pipeline model should be replaced by an extended pipeline model, which ends not with the approval of the drug or vaccine in question but with the actual delivery of the drug or other preventative or therapeutic measure to the patient at the point of need. This enables decision-makers to take evidence-based considerations into account right from the start of the process. Such considerations include early decisions on which disease to target as well as the various types of critical success factors (ranging from purely technical matters such as manufacturing capacity to socio-economic factors such as the absorption capacity of the healthcare system and the feasibility of basic hygienic measures in the environment in question) that determine whether a promising compound will enter the next phase in the drug development process.

Another key feature of the extended pipeline is the built-in coordination of the various activities involved that it implies. The pipeline no longer contains merely a dedicated R&D setup, but now embodies a complex environment consisting of people, institutions, chemical compounds, rules, (promising) drug/vaccine leads, registered drugs and vaccines, public-health-related infrastructure and health counselling. It follows that at any given point along the trajectory, each actor's next step will have to be well coordinated with those of others in the field, who might be taking similar, different, complementary or even contrary steps.

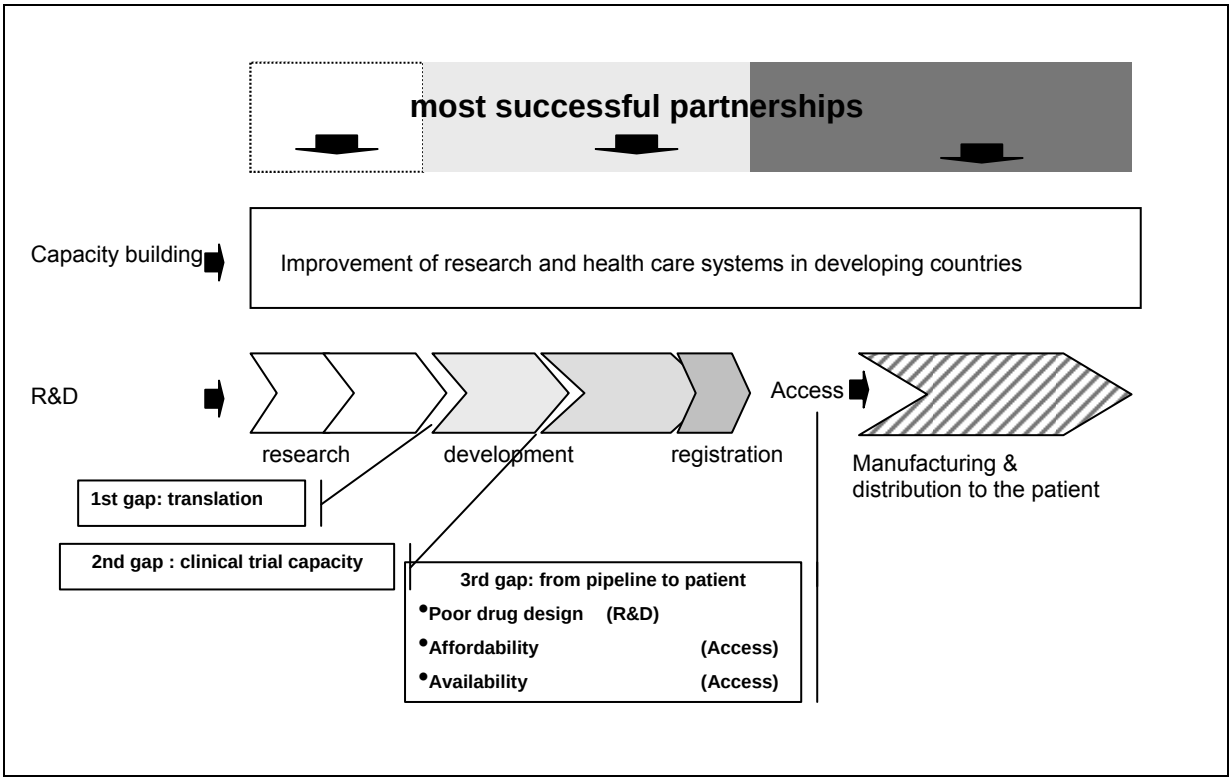


Figure: The extended pipeline (Ellen ter Gast)

The schematic representation of the extended pipeline presented in Fig. 0 clearly shows the various gaps mentioned above: that between research and drug development, the lack of clinical trial capacity and the obstacles to the manufacture, distribution and use of the drug once it has been registered.

If it may be assumed that the extended pipeline concept is a useful aid to analysis and that the gaps in the pipeline have been correctly identified, a set of crucial questions arises: how can the gaps best be bridged? What are the critical success factors to ensure optimal flow through the pipeline? What criteria must the input to the pipeline satisfy? And what parties should be involved in the different phases of the extended pipeline?

One thing that this extended pipeline model makes clear is that optimization of system performance requires feedback loops at various points along the pipeline. For example, the social and economic conditions of potential users need to be taken into account during the initial setting of research priorities. In other words, the reality 'at the end of the pipeline' should sufficiently inform the actions taken throughout the pipeline—and in fact even *before* the pipeline's point of entry.

1.8 Conclusions

The drug development pipeline model conventionally used in the pharmaceutical industry describes the steps through which a drug passes from the initial R&D phase up to and including registration and approval of the finished drug. It reflects the importance of the basic research and production processes. It is useful for improving the cost-effectiveness of a product, and can play a key role in detecting weak points in the technical process. But it does not take all necessary factors into account.

The 'extended' pipeline model widens the perspective by taking the delivery and the impact of the drugs into account too. It covers the whole range from initial policy proposals to on-the-spot therapeutic measures. The extended pipeline concept includes the traditional drug development pipeline but goes further to consider such issues as prioritization of different types of action and different beneficiaries, the training of local health personnel and the provision of the necessary infrastructure.

The extended pipeline ends not with the approval of the drug or vaccine in question but with the actual delivery of the drug or other preventative or therapeutic measure to the patient at the point of need. This enables decision-makers to take evidence-based considerations into account right from the start of the process.

In the rest of this report, the extended drug development pipeline model will be taken as a framework for analysis and discussion. However, the perspective it offers is still incomplete since it does not give the necessary insight into the last section of the pipeline – the social context in which the drugs and vaccines will function. Chapter 2 complements the extended pipeline model by focusing on this social context with reference to the Social Determinants model recently developed by the United Nations (2008).

2 The Social Determinants Model

A drug needs to have high efficacy if it is cure sick people, and it must be delivered efficiently and equitably if the sick people are to have any hope of cure. That is the 'lesson' that the extended pipeline model teaches us. However, widening the picture from the technical aspects to the delivery process of a drug still does not give us all the information we need. Further insights are necessary to explain why for example a girl who is born today in Sweden has a life expectancy of more than 80 years, while one born in Botswana will be lucky if she reaches the age of 40. This is not due only to the quality of drugs or their accessibility.

Access to drinkable water, sanitation, proper nutrition and comfortable houses; and further the working conditions, education, level of gender equality, social cohesion and lifestyle found in the country where we live all contribute in different degrees to our biological health and longevity. This is the foundation on which the Social Determinants Model (SDM) is constructed. The SDM was elaborated by the UN Commission on Social Determinants of Health in the Report *Closing the Gap in a Generation* (2008). This model, which is described in the present chapter, clearly shows the links between health and its social determinants. The content of this chapter is closely related to that of the previous one. The SDM is the other side of the coin represented by the integrated approach based on the extended pipeline model. Taken together, these two models combine 'science-based' analysis of the steps involved in the production and distribution pipeline with empirical data from the fields of epidemiology, economics and sociology.

2.1 The effect of social and economic factors on the health status

Health is often automatically associated with medicine. Medicine is the scientific discipline developed by society to restore health and cure illness. It is also automatically associated – at least in the minds of people in the affluent West - with hospitals, doctors, drugs and medical technology. There can be little doubts that these factors have a strong influence on morbidity, mortality and more broadly on the health status of the people in a given society. This assumption is thrown into context by a saying from Rudolf Virchow (1821-1902), the founder of Social Medicine: "Medicine is a social science; and politics is nothing but medicine on a grand scale".

This saying reminds us that 'medicine' (in the restricted sense) is only one of the many factors that contribute to the health of a population. The great improvements in health and life expectancy in Western countries in the 20th century are largely due to the availability of good drinking water, sanitation, improved nutrition, comfortable housing, better working conditions and higher education. Of course, antibiotics, vaccines and the whole range of other medical services available also played a role, but health at the population level is closely related to social and economic factors. In other words, patterns of health and longevity are shaped by social, economic, political, and cultural determinants (Fig. 1).

Fig . 1 - Social determinants of health

Western society is relatively affluent. Food and drinkable water are guaranteed for almost everyone, but still the mortality rates, life expectancy and morbidity are closely related to social status. Educational level and income have a strong influence on health status. Differences in educational, economic, and occupational status create differences in the quality of life that have a directly effect on health. A person's position in society shapes his or her exposure to stressors, the availability of coping resources, and lifestyle. Social factors that affect health persist, within the context of the economic and social organization (Mirowsky et al. 2000).

Western society is going through an 'epidemiological transition', characterized by the fact that the main causes of death are no longer infectious diseases but cancer and cardiovascular disease. In such a scenario, lifestyle is central for good health. Smoking, drinking and lack of exercise are correlated with high health risks and the development of chronic disease. These factors in their turn are linked to other determinants of health, in particular education. Education shapes lifestyle directly, by increasing the sense of personal control, as well as indirectly. The effects of education on behaviour (including avoidance of health risks) "more than on access to medical care, explain the beneficial impact of education on health" (Mirowsky et al. 2000, p. 55).

2.2 The Social Determinants Model

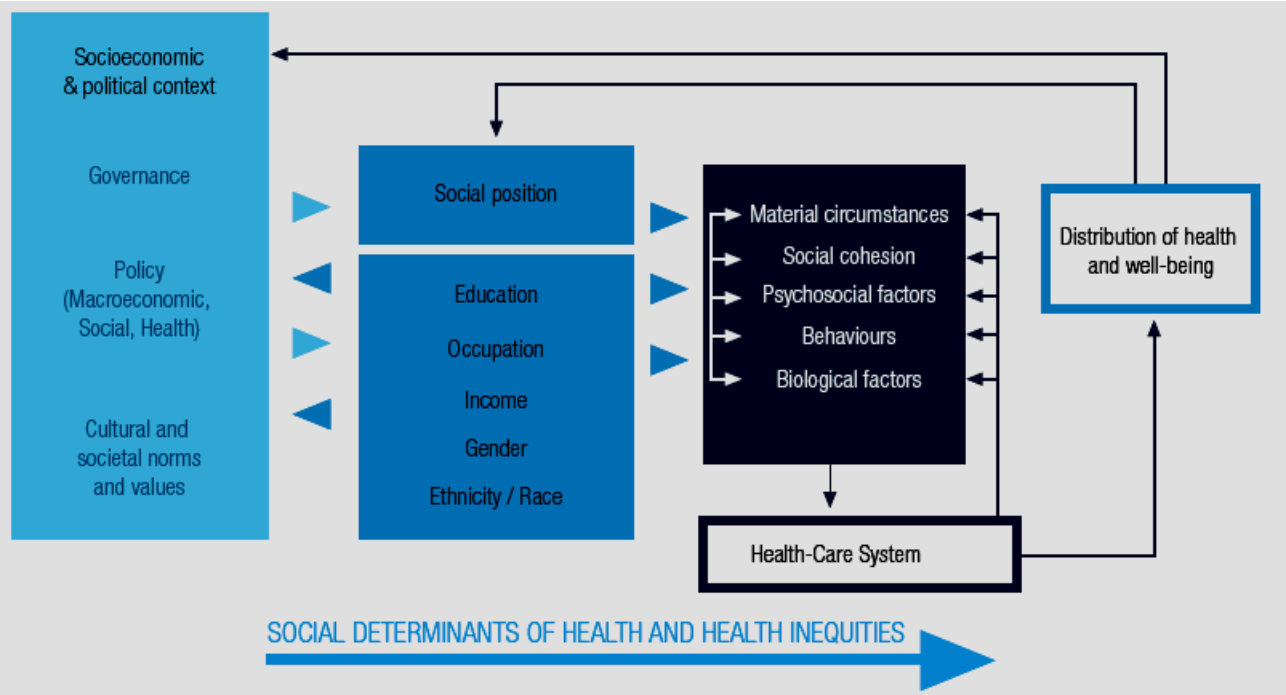
The Commission on Social Determinants of Health (hereinafter simply referred to as the Commission) was launched in March 2005 and completed its initial work in September 2008 with the publication of the *Closing the Gap in a Generation. Healthy Equity through Action on the Social Determinants of Health* (simply referred to as the Report below). It is chaired by Sir Michael Marmot, professor of Epidemiology & Public Health at University College London and director of the UCL International Institute for Society and Health, and has twenty Commissioners. The Commission brings together leading scientists and practitioners to provide evidence on policies that improve health by addressing the social conditions under which people live and work. It collaborates with national authorities to support policy change and monitor results.

Apart from drafting the Report, the main tasks of the Commission are:

- To support policy change in various countries by promoting models and practices that effectively address the social determinants of health.
- To support countries in placing health as a shared goal, to the achievement of which many government departments and sectors of society contribute.
- To help build a sustainable global movement for action on health based on considerations of equity and social determinants, linking governments, international organizations, research institutions, civil society and communities.

The Commission formulated the Social Determinants model as an instrument that would support efforts aimed at the achievement of these goals.

Fig. 2 - Conceptual framework proposed by Commission on Social Determinants of Health



The Social Determinants model is the conceptual framework used to analyse global health dynamics. The need for this model was mentioned briefly in the Conclusions of Chapter 1 (see section 1.8 above). In considering how this model could be used to support 'closing the (health inequity) gap in a generation', the Commission identified three main lines of action:

- Improve the conditions of daily life – the circumstances under which people are born, grow, live, work, and age.
- Tackle the inequitable distribution of power, money, and resources – the structural drivers of these conditions of daily life – globally, nationally, and locally.
- Measure the problem, evaluate action, expand the knowledge base, develop a workforce that is trained to think in terms of the social determinants of health, and raise public awareness about the social determinants of health.

The rest of this chapter considers various aspects of the Social Determinants model, though most of the references, quotations and data it contains are drawn from sources other than the Report.

2.3 The link between health and education

The association between poor education and poor health has been consistently observed in a number of studies and in different countries. People with poorer educational attainments have poorer health, greater disability and greater chances of death. There is a range of possible ways in which education can affect health. For example, education leads to healthy behaviour like giving up smoking and eating healthily through a greater sense of control. And higher educational attainment leads to better paid occupations which in turn results in better health and healthier lifestyles. People with high levels of education also experience better mental health, as indicated by low levels of depression and psycho-physiological malaise (Ross and Van Willigen 1997, pp. 275-97).

In the one of the most famous works on this topic (Ross and Chia-Ling, 1995), Catherine Ross and Wu Chia-Ling found on the basis of empirical data that compared with the poorly educated, well educated persons are less likely to be unemployed, are more likely to work full-time, to have fulfilling, subjectively rewarding jobs, high incomes, and low economic hardship. Full-time work, fulfilling work, high income, and low economic hardship in turn significantly improved health in all analyses. Moreover, the well educated reported a greater sense of control over their lives and their health, and they had higher levels of social support. The sense of control, and to a lesser extent support, this group experiences are associated with good health. It may therefore be assumed *that high educational attainment improves health directly, and it improves health indirectly through work and economic conditions, social-psychological resources, and healthy lifestyle*.

As a few extra years of school are associated with extra years of life and vastly improved health decades later, in old age (UNESCO 2007), it is essential that "governments provide quality compulsory primary and secondary education for all boys and girls, regardless of ability to pay, identify and address the barriers to girls and boys enrolling and staying in school, and abolish user fees for primary school" (WHO 2008a, p.58).

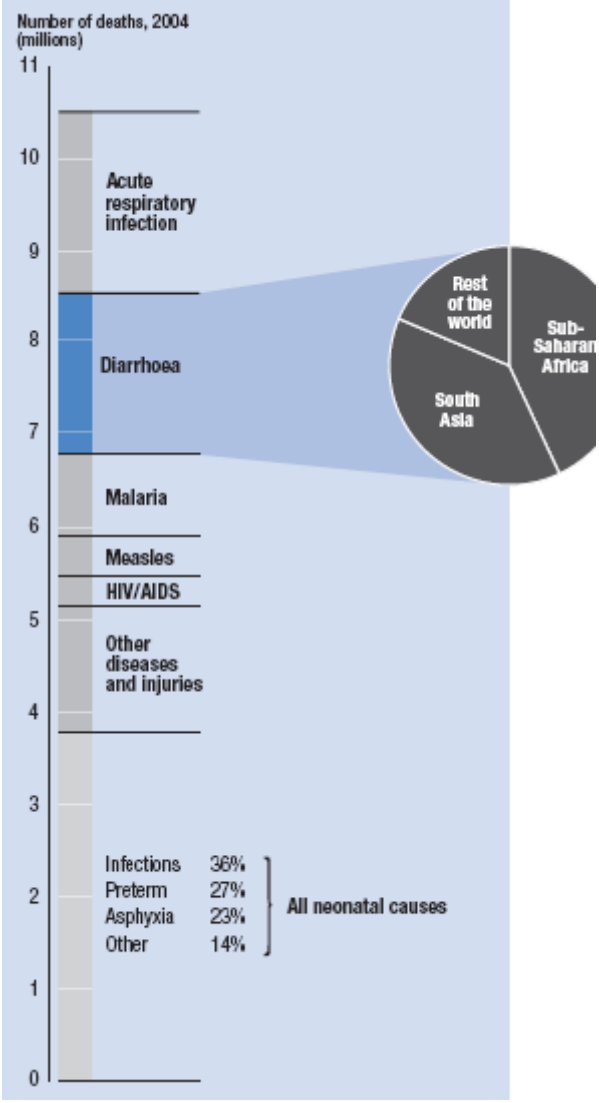
Expand and improve early childcare and education.	Achieve a 50% improvement in adult literacy rates.
Provide free and compulsory universal primary education by 2015.	Eliminate gender disparities in primary and secondary education by 2005 and at all levels by 2015.
Ensure equitable access to learning and life-skills programmes.	Improve all aspects of the quality of education.
	Source: UNESCO, 2007a

Box. 1 - UNESCO Education for all goals

2.4 Water and sanitation

Safe water and sanitation are the essential drivers needed to combat world poverty and inequality. The lack of safe water and sanitation cause more infant deaths than any other condition. Diarrhoea kills more children than tuberculosis or malaria. Infant deaths due to diarrhoea are five times more frequent than those due to HIV/AIDS. According to the WHO, 1.1 billion people in developing countries have reduced access to water and 2.6 billion do not have adequate access to sanitation.

Fig. 3 - Diarrhoea: the second biggest killer of children (WHO 2007, p. 43)



The scarcity of water should not be considered as due to physical unavailability but as the result of political processes that disadvantage the poor, stated the UNHD report of 2006 which was devoted to the Global Water Crisis (WHO 2007). The lack of safe water is rooted in institutional and political choices. There is huge inequality in access to clean water and sanitation at household level, though it should be noted that household needs actually account for no more than 5% of the total water requirements.

Occupants of high-income areas of cities in Asia, Latin America and Sub-Saharan Africa enjoy access to several hundred litres of water a day delivered to their homes at low prices by public utilities. In contrast, slum dwellers and poor households in rural areas of the same countries get much less than the 20 litres of water per person per day regarded as the most basic requirement (WHO 2007, p.2)

The access to water must be considered as a basic human right. Water determines the length of life and its quality. It is the precondition for the enjoyment of civil rights (for instance the right of economic action) and political rights (the right to dedicate time to the improvement of the community). Safe water and sanitation are fundamental for human development.

Individuals in developing countries typically spend large amounts of time collecting water, thus leaving less time for other more profitable activities such as work and education. Equity in access remains vital to all water policy, and ensuring this is a clear responsibility of the state. Privatization of the water supply has highly adverse effects on the access enjoyed by poorer households (See Box 2).

Box 2 – Water privatization in Argentina and Bolivia

Since 1993, the French company Suez-Lyonnaise has been the major partner in the privatized utility company supplying water to Buenos Aires' 10 million inhabitants, one of the largest water concessions in the world. Utility prices were raised by more than 20% after privatization. Poorer families – if connected to the supply at all – could no longer afford to pay their water bills.

In September 1999, the international water-led consortium Aguas del Tunari was awarded a 40-year concession for the water and sanitation system of Cochabamba, the third largest city in Bolivia. Water tariffs increased by up to 200% in order to cover the costs of a massive engineering scheme.

Sources: Loftus & McDonald, 2001; http://www.foe.co.uk/resource/briefings/gats_stealing_water.pdf

2.5 Gender and health

Gender inequality damages the health of millions of women, girls and children. Gender inequity is not only unfair but also ineffective and inefficient. It leads to diseases and mental illnesses through different paths: "discriminatory feeding patterns, violence against women, lack of access to resources and opportunities, and lack of decision-making power over one's own health" (WHO 2008a, p. 145).

According to the WHO[5], the socio-cultural factors that prevent women and girls from benefiting from quality health services and attaining the best possible level of health include:

- unequal power relationships between men and women;
- social norms that decrease education and paid employment opportunities for girls and women;
- an exclusive focus on women's reproductive roles; and
- potential or actual experience of physical, sexual and emotional violence.

It will be clear that women, especially poor women, are likely to be exposed to increased health risks due to the combination of a variety of factors: their chances of getting a good education are low; they run a high risk of an unexpected pregnancy at a young age; they experience difficulties in finding a job and if they do find one are likely to be paid less than men; and they are exposed to many kinds of violence... In particular, women and young girls in developing countries are likely to find themselves in a catch-22 situation in which they carry a double burden of disadvantage, since they are the ones who sacrifice their time and their education to collect water: if they neglect their task of collecting water, they and their family run the risk of falling ill or even dying of thirst; but if they take the time to collect water, they forego the education they need to ensure a healthier and more prosperous future. It is not by chance that 64% of all illiterate adults are women (495 million) (UNESCO 2006).

Moreover: "In many societies, crimes of domestic violence and rape are not even discussed are thus invisible. In most settings, however, gender alone does not define risk for such assaults on dignity. It is *poor* women who are least well defended against these assaults" (Farmer 2005).

[5] http://www.who.int/topics/womens_health/en/ (14/10/08)

Fig. 4 - Level of wages for women compared with men in selected countries (WHO, 2008, p. 146)

Figures indicate clearly the trends in gender discrimination:

- Of all adults living with HIV in sub-Saharan Africa, 61% are women;
- Smoking rates among men tend to be 10 times higher than women. However, due to recent aggressive tobacco marketing campaigns aimed at women, tobacco use among younger females in developing countries is rising rapidly. Women generally have less success in quitting the habit, have more relapses than men, and nicotine replacement therapy may be less effective among women
- up to 1 in 5 women reports being sexually abused before the age of 15.
- About 14 million adolescent girls become mothers every year. More than 90% of these very young mothers live in developing countries (WHO 2008b).

2.6 Social capital and access to the healthcare system

As we have seen in the previous sections, poverty is strongly related to disease. Material deprivation (lack of water, insufficient sanitation, difficulty in finding healthy food) has obvious consequences on health status. It has been found, however, that in many Western European countries differences in the level of income are not correlated with mortality. Other factors play a more important role in determining health status in these affluent societies: life-styles, the social support network, perceived control over one's own life and the motivation to be healthy derived from the perception of one's importance for the community (Machenbach et al. 2003).

An intriguing set of studies links income inequality (not poverty) in populations to health status. It has been shown that the life expectancy at birth is much lower in nations that provide smaller income shares to the 70 percent of the population that is least well off. In other words:

"when a relatively large share of the income goes to the people in the top 30 percent of the distribution, life expectancy for the population as a whole is compromised" (Link and Phelan 2000, p.35).

According to Ichiro Kawachi, income inequality has an adverse effect on social capital, destroying connections between people and their trust in one another (Kawachi et al. 1997).

"Belonging to a social network of communication and mutual obligation makes people feel cared for, loved, esteemed and valued. This has a powerful protective effect on health. Supportive relationships may also encourage healthier behaviour patterns. Support operates on the levels both of the individual and of society. Social isolation and exclusion are associated with increased rates of premature death and poorer chances of survival after a heart attack. People who get less social and emotional support from others are more likely to experience less well-being, more depression, a greater risk of pregnancy complications and higher levels of disability from chronic diseases. In addition, bad close relationships can lead to poor mental and physical health." (Wilkinson and Marmot 2003, p. 23)

There is a close link between social cohesion and universal access to health care services[6]. It is central for population health in general, and the health of lower socioeconomic groups in particular, that social protection systems are designed to be universal in scope. Universal healthcare systems are based on the principle that all citizens have equal rights to social protection. In other words, social protection is provided as a social right and health is not considered as a market-based commodity. Neither healthcare services nor social protection against disease are given to the poor simply from motives of pity, however:

"And because everybody benefits, rather than just one group that is singled out, universal social protection systems can enhance social cohesion and social inclusion, and can be politically more acceptable. Including the middle classes by means of universal programmes can enhance willingness of large parts of the population to pay the taxes needed to sustain universal and generous policies" (WHO 2008a, pp.87-88).

Reducing health disparities has the potential for major economic benefits resulting from a reduction both in healthcare needs and in the costs of lost productivity (WHO 2008a, p. 39). It should be clear that the healthcare system itself is a social determinant of health influencing (and influenced by) other social determinants (see Figure 5).

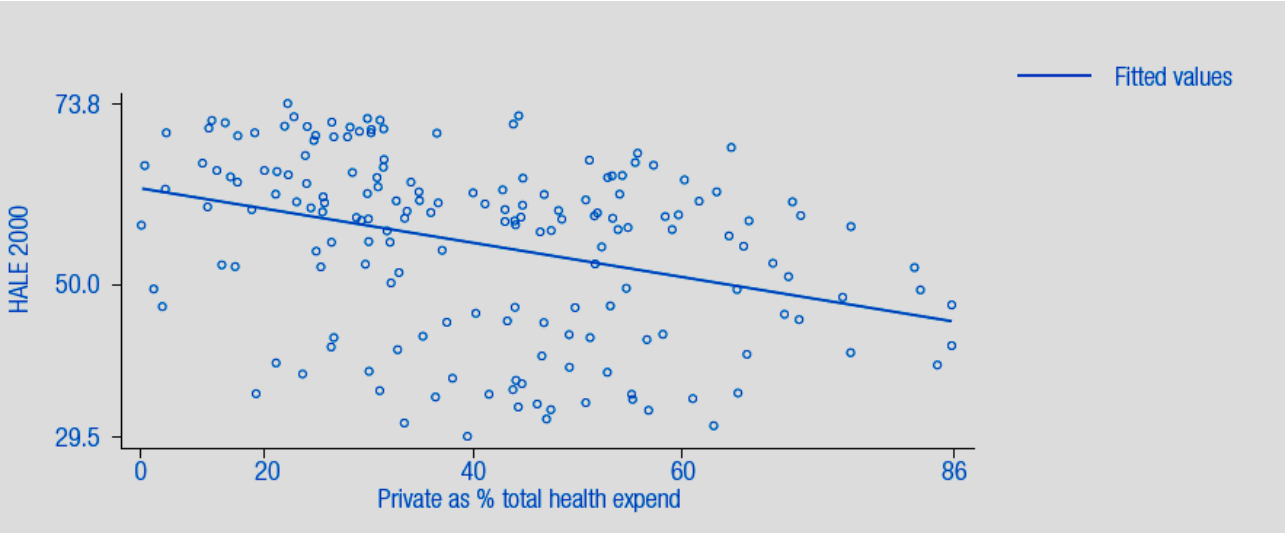


Fig. 5 – Health-adjusted life expectancy (HALE) and private healthcare expenditure as a percentage of total healthcare expenditure in 2000 (WHO 2008a, p.94)

[6] In the EU, the primary task of the Directorate General of Social Cohesion (DG III) is to foster social cohesion and to improve the quality of life in Europe for the genuine enjoyment of fundamental human rights and the respect of human dignity. DG III issued the series of publications 'Trends in social cohesion' to provide a forum for observation and analysis of the developments taking place on matters of social cohesion in the Council of Europe member states and non-member states. Each issue will address important aspects of social protection and social cohesion. A total of 19 issues have been published at the time of writing. While the subjects they cover are of great importance (retirement, labour force, immigration) none of them was explicitly devoted to health topics (http://www.coe.int/T/E/Social_cohesion/ 18/10/2008).

Improving the organization of healthcare systems may foster and strengthen inequalities within society or may conversely represent a powerful weapon in the fight against poverty and the promotion of equity. Unfortunately, the 'Inverse Care law' applies in most countries, especially those with private healthcare systems. This principle, proposed in 1971 by J.T. Hart, states that the availability of high-quality healthcare services is inversely correlated with the needs of the population (Hart 1971).

Equal access to healthcare implies that the social groups with greater healthcare needs would find more benefit from the healthcare system than other social groups. The system should therefore aim in particular at delivery of services to the most disadvantaged groups in society. There can be little doubt, however, that the more vulnerable social groups are the ones that experience greater difficulty in accessing the healthcare system. In general, they receive lower levels of assistance than the more privileged groups (Stefanini 2006). Hence, it may be concluded that it is important to study and implement monitoring systems and assessment procedures that could identify and evaluate the main inequalities in the access to healthcare services. This approach would rely on a set of healthcare delivery equality indicators, which would need to be able not only to show the capacity of the system to respond to the needs of more vulnerable people but also to signal increases in the gap between the more advantaged and the least well off.

2.7 Network governance and the community-based approach

Contemporary society has many features closely related to the ideas of risk and uncertainty, such as the multiplicity of lifestyles, the existence of differentiated subsystems and the growing interdependence between subsystems, the erosion of hierarchy in state powers and growing complexity in the delivery of healthcare services.

How can a central authority control such a complex situation? How can institutions be coordinated to minimize the risks of side-effects and threshold effects produced by their actions? What kind of strategy could replace the naive top-down approach currently common in healthcare policies? The Commission believes that introduction of the ideas and practice of network governance and community involvement might help us to deal with the complex situation sketched above.

Governance can be defined as an approach to coordination and orientation adopted by a central authority faced with a large number of social organizations and networks in a complex and risky environment. This approach is largely based on a mixture of negotiation and participation. A system of government by a ruling elite, elected and controlled by its citizens and acting directly for the common good, seems hardly feasible in a hyper-complex modern society. Network governance might be a viable alternative.

Network governance is based on network transactions rather than the imposition of top-down control. It assumes ample community participation in the work of government. Informed citizens and social organizations are invited to cooperate with government institutions in order to help the latter to take decisions and plan policies on the basis of first-hand information on the social targets on which policies are to be applied.

Classical sociological theories (Maturo 2004) suggest that people often do not perceive the risks arising from their own behaviour and are more worried about events that they cannot control – and which moreover are relatively unlikely to occur. Community involvement combined with network governance modifies individual perceptions of risk while increasing the level of trust in institutions. Mass media studies have long demonstrated that individuals are more receptive to interpersonal communication than to mass communication.

The two-step flow theory of communication suggests that a few opinion leaders who have been targeted by media communications can act as 'innovation diffusors', affecting the beliefs and behaviour of other people via interpersonal relationships (Maturo 2004).

Moreover, some risk perception studies suggest that personal and societal risk assessments are largely separate, and people do not necessarily draw personal conclusions from their general views about society. Epidemiologists, for instance, have found that individuals tend to be optimistic about their personal health care and pessimistic about health care in society as a whole (Maturo 2004). In fact, many authors have pointed out that people often worry more about low-risk activities than those associated with a higher objective risk – for example about air travel rather than driving a car. This can be explained by the general tendency to place greater weight on possible catastrophes than on more common accidents causing less damage in each individual case. Park et al. surveyed risk perceptions in 750 residents of upstate New York in 2001 and found that people who were more involved in their community held more convergent societal and personal risk judgements - for example, they would be readier to believe that AIDS could be a problem in their own lives. These findings have interesting implications for public health promotion professionals: "If community involvement increases the personal level of concern about a health issue or if it works as an antidote to people's 'unrealistic optimism' about the health risks they face, health communication campaigns could be more effective when they are accompanied by an effort to get people involved in the community" (Park, Scherer and Glynn 2001, p. 289).

To summarize: *Governance is a method of control based on community involvement and social participation, together with the devolution of state power to local agencies and social organizations. Network governance produces two important effects: it increases trust in institutions and it redefines personal risk perceptions, making people readier to assume responsibility for their own health.*

The Commission therefore concludes that:

"Empowerment for action on health equity through bottom-up, grassroots approaches requires support for civil society to develop, strengthen, and implement health equity-oriented initiatives" (WHO 2008a, p. 162).

2.8 Conclusions

The extension of the drug development pipeline discussed in Chapter 1 allows us to enlarge our perspective to include not only the technical aspects of the production of pharmaceuticals but also the delivery policy and social impact of the drugs. At the same time, the Social Determinants model dealt with in the present chapter makes it clear that the social and economic context is central in the fight against the poverty related diseases. Poverty and inequality are the main causes of disease in developing countries.

These two approaches, the Extended Pipeline model and the Social Determinants model, must thus be regarded as complementary. They can only give results if they are used in combination. The Social Determinants model tells us which actions need to be undertaken to improve the economic and social setting in such a way as to make the drug delivery policy of the Extended Pipeline more efficient.

After the description of these two theoretical frameworks – which may be considered as two sides of the same coin – it is now possible to address concrete problems. The remaining chapters of this report will therefore contain our proposals concerning EU action required to reduce the burden of PRDs.

3 Combating poverty related diseases: The European Programme of Action

What light can the theoretical frameworks presented in Chapters 1 and 2 – the Extended Pipeline and the Social Determinants model – throw on the essential strengths and weaknesses of current EU policies on PRD's? Which actors could play a decisive role in reducing the pharmaceutical gap in the developing countries? What competences and expertise should the European organizations involved in the struggle against PRDs possess? What are the best practices?

In an attempt to answer to these questions, we will focus on the remarkable role played by two programmes: the European and Developing Countries Clinical Trials Partnership (EDCTP) and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). It will become clear below that the most successful actions against malaria, HIV/AIDS and tuberculosis are the result of an integrated approach based on the involvement of African countries in synergy with input from EU and other agencies. However, while the solutions to some problems may seem to be on the horizon, evidence may be found in the review given in the rest of this chapter of the persistence of at least four types of gaps in the fight against PRDs.

3.1 European and African countries working together for Health in the EDCTP

In response to the UN call for action in September 2000 (see section 1.1 above), the challenge of combating poverty related neglected diseases[7] has been taken up by the European Community. In 2001 the Commission of the European Communities issued its *Programme for action: Accelerated action on HIV/AIDS, malaria and tuberculosis in the context of poverty reduction.* The programme was intended to establish

..a broad and coherent community response, over the period 2001-2006, to the global emergency caused by the three major communicable diseases, HIV/AIDS, malaria, and tuberculosis, which most affect the poorest populations and which undermine global health (COM 2001, p.2).

As part of this programme for action, the EU launched its Sixth Framework Programme (FP6) in 2001. The FP6 ran from 2002 to 2006. The EU allocated a total of € 400 million to HIV/AIDS, malaria and tuberculosis, of which € 200 million was reserved for the European and Developing Countries Clinical Trials Partnership (EDCTP) (EC DG Research 2007, p.8).

The EDCTP was set up in 2003 as a European response to the global health crisis caused by the three main poverty-related diseases. Its mission is 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.

The EDCTP supports multi-centre projects which combine clinical trials, capacity building and networking. The aim of integrating these three activities is to ensure that the developed capacity is utilized to successfully conduct the clinical trials in a sustainable way. The basis of the EDCTP is partnership (EDCTP website http://www.edctp.org/).

[7]In line with the Millennium Development Goals formulated by the UN in September 2000, the EU programme of action focuses primarily on HIV/AIDS, malaria and tuberculosis. A conference was organized in November 2006 by the European Commission, Research Directorate General, Directorate of International Scientific Cooperation with the support of the European Parliament to highlight the importance of action on the other neglected infectious diseases; see also http://teamwork.intbase.com/0606_02/.

The increased funding of the programme for action means that since 2002, the EU has quadrupled its overall annual support for the fight against PRDs as compared to the average support in the years between 1994 and 2002. One of the aims of the FP6 is to improve the access, affordability, and availability of treatments and vaccines for HIV/AIDS, tuberculosis and malaria in developing countries (EC DG Research 2007, p.7), by:

"structuring and integrating European research into a pipeline of projects ranging from early discovery to clinical testing of drug and vaccine candidates for each of the three diseases."

In 2004, the EC presented its vision for a coherent European policy framework for 2015 to the European Parliament (COM 2004). The report *A coherent Policy framework for external action to confront HIV/AIDS, Malaria and Tuberculosis* stated that:

"The EC has successfully cooperated across policy areas of development, humanitarian aid, trade and research towards coherent external action. Activities in different policy areas can reinforce each other and produce greater synergy. This is the added value of the EC, and goes beyond what EU Members States can do individually. [..] The EC also added value in its ability to convene, represent and defend a common European position globally, thus improving coherence in global governance" (COM 2004, p.7).

In 2005, the EC communicated its future plans in the report *A European Programme for Action to Confront HIV/AIDS, Malaria and Tuberculosis through External Action* (*2007-2011)* (COM 2005). This report reviewed the strategy for the period 2007-2011, including a wide range of activities such as the reinforcement of political dialogue to support country-led strategies to confront the three diseases, capacity building, the implementation of new regulations aimed at affordability of medicines as well as the formulation of a set of innovative responses to the human resource crises for health providers. The Programme for Action also includes a number of proposals aimed at drug development, in the following terms:

"The EC will support the research and development of new tools and interventions through projects designed to accelerate the development of new vaccines, drugs, microbicides and diagnostic tools for resource-poor settings. The EC will encourage the participation of research organizations and institutions from disease-endemic countries in collaborative research projects with European partners. The EC will provide support for the EDCTP while urging European countries, private charities and industry to provide significant funding and expertise for this initiative. In its dialogue with participating countries and companies, the EC will advocate the inclusion of clauses on affordability, intellectual property rights (IPR), manufacturing and regulatory approval. The EC will provide support for social-behavioural research, epidemiology and operational, health-systems and applied research, and cost projection studies – including community capacity and preparedness to participate in clinical trials and to introduce new tools and interventions rapidly, once developed and approved" (COM 2005, p.9).

3.2 EDCTP strategy and Euro-African networking

The EDCTP has three key strategies for speeding up the development of new drugs and vaccines (Mgone 2007):

Project integration: linking together and adding value to existing projects funded by individual member states and developing new EDCTP projects through the coordination of member states' national programmes.

Institutional collaboration: at the level of national research institutions, the EDCTP seeks to forge alliances between European research institutes and their African partners to develop strategic joint activities in training, research and capacity development.

Coordination of national funding: the EDCTP promotes and facilitates the coordination and pooling of resources at the level of national ministries and funding agencies by encouraging core funding of EDCTP activities, together with development of joint research calls and funding policies that remove barriers to cooperation between individual member states.

Moreover, to initiate and promote more effective European and African networking, the EDCTP has established two constituencies, the European Network of National Programmes (ENNP) and the Developing Countries Coordinating Committee (DCCC). The ENNP consists of European networking officers (ENO) appointed by each EDCTP member state to facilitate their country's participation in EDCTP networking and coordination activities. Part of their mandate is to update the inventory of national activities and partnerships that lie within the scope of EDCTP activities. They identify gaps, overlaps and potential synergies between the different national programmes, compare national funding mechanisms and develop proposals for European networking strategies, including tools, consortia, incentives and funding allocations. The DCCC is an independent advisory body of prominent African scientists, health professionals and policy makers. It is particularly involved in the identification of the institutional and human capacity building needed in Africa. It also disseminates information to scientists in developing countries and develops strategies and actions to improve coordination between its members and other partners participating in the EDCTP, including national governments, WHO and other international organizations.

Looking ahead, EDCTP is establishing, through DCCC members and site visits, a database of African centres including information on capacity for conducting clinical trials, existing links between African institutions and European member states as well as the African contributions to the partnership. Since similar information is being collected by other organizations, notably the ongoing effort by the Multilateral Initiative on Malaria (MIM), the EDCTP will continue to engage these networks. Last but not least, the EDCTP plans to support the creation of several 'nodes of excellence' in Africa, with an integrated approach aiming at the establishment of regional nodes of excellence with particular emphasis on reference laboratories and data management centres.

3.3 PRD Research in the Seventh Framework Programme (FP7)

In 2007, the FP6 was followed by the seventh Framework Programme (FP7). Unlike the FP6, the FP7 also includes research programmes on PRDs other than HIV-AIDS, tuberculosis and malaria. In the coming five years (the programme runs from 2007 to 2011), the FP7's research programme:

".. will focus on an integrated approach for the development of preventive, therapeutic and control tools for neglected infectious diseases: diseases caused by Trypanosomatidae species and a wider range of vector-borne diseases, as well as other neglected infectious diseases, including childhood infections" (source: EU website http://ec.europa.eu/research/health/poverty-diseases/call-for-proposals_en.html).

In addition, the EU will undertake studies to establish a priority list of pull incentives to encourage the pharmaceutical industry to develop drugs for developing countries and select a number of public-private partnerships, and global initiatives. The underlying principles for country strategies to confront the three diseases dictate that:

"Strategies should be evidence-based and represent an appropriate policy-mix, including information, prevention (e.g. condoms and LL-ITNs [long-lasting insecticide-treated nets]), harm reduction (e.g. needle exchange for injecting drug users), vector control measures against malaria (e.g. environmental and sanitation measures and indoor residual spraying with DDT), treatment and care, and impact alleviation. Information and prevention remain crucial components of any strategy to halt the spread of HIV/AID, malaria and TB. […] Inclusion of strategies into MDG [Millennium Development Goals] -based poverty reduction programmes should be promoted in developing countries" (COM 2005, p.12)

Taken together with the EU Programme for Action, the FP7 represents an ambitious initiative to tackle a highly urgent and complex challenge.

3.4 The role of the TDR in the struggle against poverty related diseases

The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) was set up in 1975 within WHO as its Executing Agency to marshal research and capacity-building resources in the fight against infectious diseases of the poor, with the aim of improving the health of poor populations and to eliminate these diseases as obstacles to social and economic development. The TDR has done its best to play its role effectively and has developed tools and strategies through appropriate partnerships (TDR 2008).

The global research effort on infectious diseases of the poor is however still diverse and fragmented.

Some areas, such as anti-malaria and TB drug development, are well covered and there is little need for the TDR to support research in these areas. But other areas are neglected even though they are critical for the overall impact of the global research effort. These include the interfaces between major research domains, e.g. translational research between basic research and product development, research on the effectiveness of interventions between product development and intervention policy, and implementation research between research and large-scale disease control. Research at each of these interfaces is absolutely vital: translational research to feed the product development pipeline, intervention effectiveness research to inform policy-makers of use to which the drugs can be put and implementation research to help ensure that the drugs or other treatments reach the intended target. The need for implementation research is especially great given the difficulties that healthcare systems and disease control programmes encounter in achieving adequate coverage with the available resources. Without significant research activities at these interfaces, the overall global research effort will fail to deliver the intended public health impact.

The TDR's vision for the next 10 years is to foster:

An effective global research effort on infectious diseases of poverty, with special reference to the countries where these diseases are endemic.

The TDR is uniquely placed to make this vision a reality in collaboration with other partners in the global research community, but it will have to develop a new style of operation if it is to be successful. The TDR will have to act much more as a facilitator helping all partners to optimize their collective research effort in the fight against infectious diseases of poverty and assisting countries where the diseases are endemic in playing a leading role in this effort. The TDR is enabled to play such a stewardship role by its close links with the countries concerned, the scientific community and all co-sponsoring agencies and by its position within the WHO. The TDR is seen as a programme that combines scientific competency, networking and experience, with a governance system that provides for equal participation of the countries where the diseases are endemic at decision-making level.

3.5 Conclusions

The above overview highlights the key role played in particular by the EDCTP and TDR in the fight against poverty related diseases by EU and global organizations, but at the same reveals four main gaps which need to be bridged (as mentioned in section 1.5 above, three of these gaps had already been identified by Bernard Pécoul):

1. the gap between pharmaceutical improvements and social factors related to the persistence of PRDs (*the Science/Society Gap*). As will be made clear below, this Report calls for closer coordination between a science-based approach and a selective focus on the social context;
2. the fact that participation in the fight against PRDs does not help for-profit organizations to raise their competitiveness on the market (*the Policy/Reality Gap*). There is a need for closer links between public institutions and pharmaceutical companies to address this problem;
3. the need to strengthen alliances between European research institutes and their African partners to develop strategic joint activities in training, research and capacity development (*the Euro/African Research Gap*). However, this gap is partially bridged by the EDCTP;
4. the difficulty sometimes experienced in the concrete implementation of well planned projects (*the Central Planning/Local Implementation Gap*). There is a need to recruit local key informants in developing countries to provide vital feedback for top-down initiatives.

4 Lessons for designing an integrated drug delivery model

Given the four gaps identified in Chapter 3, what are the main issues that need to be addressed in EU policy on PRDs? The present chapter focuses on three groups of issues related to different aspects of the extended pipeline model. Firstly, design issues encountered at various points along the extended pipeline. These concern the way in which the end-user can be borne in mind during decision-making on such matters as prioritizing target diseases and planned activities. Secondly, coordination issues that may be visualized as situated on the axis at right angles to the extended pipeline as pictured above. It is crucial to ensure proper coordination between the different parties involved in activities at any given point along the pipeline. Here again, the interests of the end-user must never be lost sight of. And thirdly, issues concerning the integration of the design and coordination aspects. As will be shown in Chapter 5, the nature of the integration called for is closely related to the above-mentioned four gaps.

Most of the content of the present chapter is derived from the report of the expert meeting organised by the Rathenau Institute (See Annex 1)

4.1 Design issues

How can we ensure that due attention is paid to 'neglected' diseases?
The first step in the prioritization of the delivery of drugs and other medical services is identifying the diseases you want to focus on. The EU's Sixth Framework Programme (FP6) followed the United Nations Millennium Goals in focusing on HIV/AIDS, malaria and tuberculosis and neglecting other infectious diseases**.** This has been a matter of controversy within the EU. In order to address this issue, the European Commission organized a conference chaired by John Bowis, MEP for London and Rapporteur for the European Parliament's 2005 report on neglected diseases. The authors of the report on this conference stressed that:

"while 'neglected diseases' are not as high profile as the 'Big Three' diseases – HIV/AIDS, malaria and tuberculosis – […] millions of people, mainly poor people in the developing world, are suffering from a range of other infectious diseases that also need due attention. These diseases not only affect people's health but are also damaging in wider socio-economic terms." (EC DG Research 2006 p.6)

What is the point of developing new drugs when healthcare systems are failing?
When a specific disease in a developing country is a candidate for increased attention, the next question is of course where or how to focus the available resources: do you want to concentrate on prevention or cure, or on patient groups requiring special treatment such as mothers or children? Prevention is key in the fight against PRDs. Sometimes, vaccination is the answer. But in other cases, such as those involving waterborne diseases including pneumonia, diarrhoea and malaria, investment in water supplies, sanitation and infrastructure as well as raising awareness of the links between health, clean water, sanitation and hygiene are critical components of the combat strategy as described in section 2.4 above.

The poor healthcare infrastructure (ranging all the way from human resources and diagnostic tools as well as the provision of therapeutic services) in developing countries constitutes a major barrier to progress. For example, it seriously hampers the effective distribution of drugs (Singer 2007, Lob-Levyt 2007). Even when newly developed high-efficacy drugs are available, they remain ineffective in the absence of clean drinking water to take the pills with.

The shortage of trained healthcare providers undermines efforts to scale up the delivery of prevention, treatment and care services. Lob-Levyt claims that these problems are quite common:

> ".. there is a tendency amongst donors to focus on disease specific issues at the expense of broader reinforcement of health systems" (Lob-Levyt 2007, p.171).

How to bridge the translational research gap between basic research and product development?

The EU Programme for Action focuses on R&D for new drugs and similar medical interventions, on the basis of the urgent need for new drugs, vaccines and diagnostic tools. But, as mentioned in previous chapters, drugs for use in developing countries need to be judged by other performance metrics (clinical efficacy for the target group, route of administration, dosage regimen, safety, cost of treatment etc.) than those applicable in the Western world. Hence, when designing drugs for developing countries

"emphasis should be placed on understanding the product profile of drugs required for the various neglected diseases" (Hopkins et al. 2007, p.167).

It is crucial to investigate the effectiveness and appropriate use of new and existing products under conditions of real use, since

"many products that have successfully completed the R&D process have failed to achieve their full potential impact because of implementation problems that impeded access" (TDR 2007 p.12).

One of the most neglected research areas is the development, evaluation and improvement of new interventions and intervention strategies in real-life settings and within a public health context. This research is crucial, and provides disease-endemic countries with the evidence they need to make informed health policy decisions on which products to use, how to use them, when to use them and how to optimize their public health utility (TDR 2007 p.11).

Thus, we can identify a translational gap between the specific restraints on drug design for developing countries and the drugs actually developed.

4.2 Coordination issues

A leading role for TDR?

It will be clear that, in addition to evidence-based priority setting, the coordination of activities between the different parties dedicated to combating neglected PRDs is of key importance. This also applies to the Seventh Framework Programme (FP7).

We need partnerships in health research because diseases cover so many areas – the EU cannot, and does not, act alone. For FP7 to be truly successful, international scientific cooperation will have to play a greater role than has been the case in the past. This will strengthen the EU research through better links – both scientific and political – and help us to face common challenges (Potocnik, 2007).

In order to prevent ineffectiveness due to fragmentation and lack of involvement of disease-endemic countries, the EU must coordinate all their activities with those of other global operators. The WHO/TDR currently seems to be the most likely candidate for such a coordinating and/or advisory role in partnership with the EU.

At least, this is how the WHO/TDR sees it:

"TDR needs to be a facilitator that supports all partners in optimizing their collective research effort against infectious diseases of the poor and that assists disease-endemic countries in playing a leading role in this effort" (TDR 2007, p. 6)

The IFPMA (*International Federation of Pharmaceutical Manufacturers and Associations*) subscribes to this central role of the TDR:

"The TDR programme plays a vital and unique role in helping to coordinate, support and encourage global research and development efforts in this important area. […]

Research based pharmaceutical companies have been working closely with the TDR since its inception in 1975 and will continue to do so. The TDR network model brings together academic research groups and industry, providing an environment which enables companies to make available a broad range of in-kind resources, with the ultimate goal to promote the development, availability and accessibility of new medicines to combat diseases that disproportionately affect poor people living in developing countries." (IFPMA News Release of 25 January 2007)

Mary Moran, Director of the Pharmaceutical R&D Policy Project at the London School of Economics and author of *A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs we Need*, also judges the WHO/TDR programme favourably: "overall, WHO/TDR-industry collaborations have had a better health outcome than industry-alone projects." She emphasizes, however, that the positive results of WHO/TDR involvement may be due to the fact that this programme primarily participates in Phase IV implementation studies (Moran 2005, p.47).

Partnership with industry: possible ways of bridging the policy/reality gap

The reason most commonly suggested for the failure to control neglected diseases is the existence of the global market mechanism. Pharmaceutical companies are powerful players in that market and they tend to be disinclined to invest in drugs for poverty related diseases, since they foresee a poor return on investment when the patients to be treated, or the national health authorities in question, are unable to pay top prices for the products needed. As a result, almost one-sixth of the world population is currently affected by PRDs for which there is no effective, affordable cure (Singer 2007, Hopkins et al. 2007).

Various incentives – which may be subdivided into 'push' and 'pull' mechanisms - have been proposed to encourage pharmaceutical companies to enter the developing countries healthcare market.(Callan and Gillespie 2007).

Push mechanisms increase investment in research at the start of the innovation pathway: for example, by subsidising the costs incurred when developing products for unprofitable or unpredictable mechanisms. […] The most promising new push mechanisms involve public/ private PDPs [Product-Development Partnerships], which optimise leads, select candidates and bring products through clinical trials. (Callan and Gillespie 2007, p. 164)

Pull mechanisms – such as advanced market commitments (AMCs), patent extensions, prizes and patent buyouts – are designed to provide incentives for the development and manufacture of usable technologies towards the end of the innovation pathway. They motivate investment by guaranteeing a reward for the product after the completion of its development phase (Callan and Gillespie 2007, p. 164)

However, the question is whether these push and pull mechanisms are at all effective. The most common approach used by multinational companies to cut R&D costs is increasingly to work with a public-private partnership (PPP) at some point in the R&D process (Moran 2005, p.13). A major part of the research on neglected disease drug development by multinational companies is already, or soon will be, conducted under a partnership model. Two years after the publication of Mary Moran's report, the IFPMA stated that:

Public-Private Partnerships have now become a distinctive feature of the healthcare landscape in low- and middle-income countries. Carrying the burden of some of the world's worst diseases whilst also facing severe shortages of all kinds, these countries need very broad health interventions, which experience has shown can only be delivered through multi-sector partnerships (IFPMA 2007, http://www.ifpma.org/index.php?id=180).

Remarkably, all multinational companies engaged in neglected disease R&D that were interviewed by Moran and her colleagues declared that current government activities played no role in their decision to go down this road (Moran 2005, p. 17). This contrasts with the policies proposed by funding organizations and public authorities such as the EU, which are largely based on economic incentives. Moran refers to this mismatch between policy and industry motivations as the policy-reality gap (ibid., p 17). According to these authors, authorities have not yet adapted their policies to the new realities of private initiatives:

"We note that commercialising low-value neglected disease markets, for example through the use of advanced purchase commitments or roaming patent extensions, is likely to increase industry activity (particularly small companies), but at the cost of curtailing these positive behaviours [participation in PPP's on a not-for-profit basis] and returning R&D to the more secretive and non-collaborative approaches that are characteristic of commercial R&D" (Moran 2005, p. 12) "[..] many current proposals seem designed to encourage industry away from PPPs and toward profit-driven in-house neglected disease drug development." (Moran, 2005, p.39)

4.3 Integrating design and coordination: working together with developing countries

Many authors stress the importance of coordination with the developing countries. According to Lob-Levyt, for example:

"The international community has been successful in mobilizing financial and political support for HIV/AIDS prevention and treatment, and for vaccines for children. It has been less effective, however at uniting around a vision and strategy to tackle the more fundamental challenge – the building of an integrated delivery platform across the public, private and civil-society sectors in the poorest parts of the world" (Lob-Levyt 2007 p. 171).

The TDR also sees the lack of research capability and research leadership in developing countries as a critical component of the vicious cycle (TDR 2007, p. 4). This point had already mentioned by the EU, who stated in 2003 that more effort is needed to provide regular and structured consultation with developing countries. This still remains a challenge for the EU Programme for Action, however. The independent external reviewers of the EDCTP are critical about the collaboration with the selected African developing countries, as illustrated by their repeated insistence that the African presence in the EDCTP and its decision-making process should be enlarged. These independent external reviewers further point out that the EDCTP programme tacitly assumes that investments in selected African institutions will lead to sustainable capacity strengthening. However, experience has shown that such projects tend to fail unless there is clear involvement of the host government, to provide assurance of continuing support when external aid ceases. (Van Velzen et al. 2007 p.21)

4.4 Conclusions

Consideration of the four gaps indicated in Chapter 3 led in the present chapter to a review of the main issues to be addressed in the EU's PRD policy. Our conclusions may be summarized as follows.

Firstly, health professionals from the developing countries need to be much more closely involved in the pharmaceutical design process at different points along the extended pipeline. Such involvement is crucial not only in settling priorities but also in research activities and the assessment of the new drugs.

A strategy based on strong integration of the roles of the main players would overcome the current fragmentation of activities. Representatives of the developing countries can and should play a leading part at all the stages of the process – from design and manufacture to delivery and use on the ground. Paradoxically, people from developing countries have the know-how needed to make the most advanced technologies work effectively in real settings.

Moreover, drug efficacy needs to be measured in real life settings. It is of crucial importance to study the effectiveness and appropriate utilization of new and existing products under conditions of real use. Drugs for use in developing countries need to be judged by other performance metrics (clinical efficacy for the target group, route of administration, dosage regimen, safety, cost of treatment etc.) than those applicable in the Western world.

Furthermore, there is a pressing need for drugs to be made more readily available in developing countries. The pull and push mechanisms discussed in this chapter should help to encourage pharmaceutical companies to enter the developing countries healthcare market.

A desirable scenario could involve the TDR playing a stewardship role in coordinating the activities of all parties to optimize their collective research effort directed against infectious diseases of the poor, and especially in boosting the involvement of disease-endemic countries in this process.

The discussion given in the present chapter has pointed out some ways in which the four gaps mentioned at the end of Chapter 3 could be bridged. More concrete proposals are given in Chapter 5.

5 Recommendations

We have seen in the previous chapters how a lack of drugs, difficulties in their distribution, constraints in the access to healthcare services, poor social and economic conditions can undermine the health of the population in developing countries and their social advancement. How can the EU make sense of this complex and multidimensional situation and on this basis make a meaningful contribution to closure of the pharmaceutical gap and ultimately to the enhancement of global health?

First and foremost, the fight against PRDs needs to be conducted at different levels. Obstacles in the conventional drug distribution pipeline must be surmounted. The pipeline must be extended by including the distribution and delivery phases in addition to R&D and manufacturing, and feedback needs to be built in so that decision-making during the initial stages of the pipeline can be much better informed by knowledge of what goes on at the end. But above all, policy-makers must acknowledge that the development of drugs to combat specific diseases and thus further global health, important though this aim is, should not divert attention from the most essential goal of relieving world poverty.

On the basis of the considerations given in the previous chapters, in particular the Extended Pipeline model and the Social Determinants model developed there, we will conclude this report with a number of recommendations on how the European Union can better define the problems involved and plan improvements that lie within its scope.

5.1 The need to bridge the Science/Society gap

The tremendous infant mortality rates, low life expectancies and high morbidity in the developing countries are largely due to poor social and economic conditions such as lack of drinkable water, poor sanitation, low educational levels, poverty, inequality, gender violence and unequal access to health services. Science-based improvement in the delivery of drugs is central in the fight against poverty related diseases, but the epidemiological mainframe will not change unless the underlying economic and social causes of the poor conditions are dealt with.

The EC should therefore work together with the TDR (UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases) to stimulate a broad understanding of the social and economic context of the persistent PRDs. Measures against PRDs should be based on a combination of a science-based model and the Social Determinants model described in Chapter 2 of this report. So far, there is little coherence between these two approaches – a situation described at the end of Chapter 4 as the Science/Society gap. A major contribution to bridging this gap would be extensive consultation between representatives of the UN Commission on Social Determinants, the UN Commission on Human Development, the EDCTP and TDR to hammer out a common viewpoint.

5.2 The focus and priorities of the EU's PRD policy

Since social and economic factors play a central role in determining the health of a population, PRDs cannot be addressed exclusively by developing and supplying drugs. Integration of medical, healthcare and social services on a community-wide basis is essential for success in the fight against PRDs. Strengthening of community-based approaches to the delivery of drugs will play a key role here.

Poverty cannot be eradicated in the short term, but actions to improve social and economic conditions with the ultimate aim of improving population health should have the highest priority. Healthcare systems can only be reinforced by close collaboration with the political and social institutions of the developing countries concerned. Projects tend to fail unless there is clear involvement of host governments, providing an assurance of continuing support if external aid should cease.

EU policy does not lack attention to the improvement of health, but in the combat against PRDs *prevention* should be the key. It might be appropriate in this connection to set up a commission with a flexible remit, charged with the formulation of proposals for the improvement of the healthcare infrastructure in developing countries.

The primary aim of the EU Framework Programme (currently in its 7th edition), which forms the context for the EU's current activities in the field of PRDs, is to raise the competitiveness of European health-related industries and businesses, while the fight against PRDs is inherently a non-commercial undertaking. Since work on PRDs does not take place in a competitive market, it is unlikely to contribute to increasing the competitiveness of European businesses. The current requirement that R&D projects on PRDs within the 7th EU Framework Programme should make such a contribution represents a barrier to their success, and the EU should consider lifting this constraint for projects of this type.

In view of the EU's limited budget for PRDs, a strategic choice should be made of a limited number of domains within this broader field where the EU could be an important player.

5.3 Enhancing the role of developing countries in the extended drug delivery pipeline

To ensure the success and sustainability of many North–South collaborative programmes, developing countries need to be empowered to participate fully in such activities and to act as co-owners. One of the ways the EDCTP is already supporting this approach is by demanding the input of developing countries in capacity development and networking in applications for clinical trial grants.

Joint planning and prioritization of the research agenda by all stakeholders is essential to ensure better coordination and focus in clinical trials. This is particularly true of international collaboration - especially when this involves North–South partnerships - where there is often a diversity of needs, expectations and capacities between partners. It has been suggested in this connection that "One approach to a joint strategy could be planning a series of distinct but complementary clinical trials, each asking different questions. In the end, the answers will complete the big picture."

EC contributions to the funding of research in the fight against PRD should be guided by the principle of the integration between EU and African efforts. In order to foster a genuine partnership and enhance local clinical research capacity, EU-African projects should have African scientists based in Africa as their principal investigators.

5.4 EU participation in partnerships as prerequisite for successful drug delivery

Finding the right partners is generally acknowledged to rank among the biggest challenges in any results-oriented R&D effort on PRDs. This requires tailor-made partnerships, all along the extended drug delivery pipeline, with due emphasis on the illness to be addressed, possible shortcomings of the healthcare system in question and a host of other factors.

Despite the EU's declared intention to work in partnership with PPPs (public-private partnerships), EU involvement in such partnerships is still negligible in practice and needs to be markedly increased. To ensure the success of R&D projects in this field, the EU should partner industry all along the extended pipeline.

Moreover, in order to prevent ineffectiveness due to fragmentation and lack of involvement of disease-endemic countries, the EU must coordinate all their activities with those of other global operators. The WHO/TDR currently seems to be the most likely candidate for such a coordinating and/or advisory role in partnership with the EU.

5.5 Need for a clearly defined strategy

Serious EU participation in the fight against poverty related diseases demands formulation of a sound strategy laying down clear goals, policies and actions. Within the context of the 6th Framework Programme, the EU Programme for Action on PRD diseases was guided by a "coherent European policy framework for external action to confront AIDS/HIV, malaria and tuberculosis".

However, this programme for action has not been updated since 2005. This means that there are no clearly defined guidelines for EU policy-making on PRD in the 7th Framework Programme, which has now started..

A new strategic Programme for Action, and the human resources to drive it, seems a prerequisite for the EU to be proactive and to remain in tune with other actors. This would have multiple advantages, as spelled out in the present report. Moreover, keeping the Programme for Action up to date requires an ongoing learning process. We believe therefore that the EU should put the development and institutionalization of a coherent Programme for Action on PRDs high on its list of priorities.

5.6 Need for a strong support structure as a base for the Programme for Action

The science-centric idea that PRDs can be addressed simply by developing and supplying the right drugs is misleading. Even in the most developed countries, drugs account for no more than 20% of total healthcare expenditure – much more is spent on healthcare systems, for example. Indeed, the lack of adequately trained health workers and an adequate healthcare infrastructure is currently a severe constraint on the effective use of drugs in many developing countries.

This indicates that an effective strategy in the fight against PRDs must be based on an integrated approach, aimed both at the development of new drugs, vaccines and diagnostic tools and at improving healthcare systems. In 2005, the EC communicated its future plans in the report *A European Programme for Action to Confront HIV/AIDS, Malaria and Tuberculosis through External Action* (*2007-2011).* The organizational structure required to support the execution of this strategy is however still lacking.

The EDCTP does address capacity building at the level of the recipient country and its institutions, but does not include the reinforcement of national healthcare systems in this approach. The independent contribution of the EDCTP in such matters as drug regulation and ethics reviews is, however, still useful in its own right.

5.7 Improving the coordination of EU Directorates-General

The coordination of the activities of the EU Directorates-General for External Aid and Development, Trade and Research still leaves much to be desired. Efforts aimed at improving such coordination should take place in the context of the EU Programme for Action on PRDs. Regular inter-departmental meetings on PRDs are essential if the EU is to achieve its aim of becoming a learning organization. In addition, coordination of EU activities with those of other parties with the aim of securing added value should be a primary concern for within the framework of the EU's PRD policy.

5.8 Evaluation of actions and results

All global efforts in the fight against PRDs should be periodically monitored and evaluated in two main areas: biomedical activities and activities aimed at improving social and economic conditions.

Three main types of questions need to be asked in this connection: What resources are needed, and what have been deployed? What activities are required, and what have been undertaken? And what is the impact of the activities undertaken? Important performance indicators in this context are the degree of integration achieved between the science-based and social-determinant approaches, the involvement of African scientists and the extent to which community based activities have been fostered.

The evaluation should be performed by a committee comprising a selected group of scientists and professionals from different fields such as epidemiologists, economists, sociologists and a variety of biomedical scientists. Representatives of the EDCTP, TDR, UN Commission on Social Determinants, UN Commission on Human Development could also be included.

5.9 Need for a proper balance between the "Big Three" and neglected diseases

Many authors see the "Big Three" diseases - malaria, AIDS-HIV and tuberculosis – as competing with the "neglected diseases" when it comes to the allocation of funds for the fight against disease. There is a need to emphasize the large number of facts that argue against this negative viewpoint.

For example, it is often much easier (and less expensive) to treat neglected tropical diseases than the "big three". Interventions against neglected diseases could dramatically improve the standard of living across the developing world, and would serve both to bring nations closer to the Millennium Development Goals set by the UN in 2000 and make interventions against the "big three" diseases a bit easier.

Rapid-impact interventions would directly reduce the transmission of tropical infectious diseases. This would have a significant economical impact on the fight against the "big three". In fact, actions aimed at improving social and economic conditions would also have a preventive effect on PRDs and other neglected diseases, since all diseases of the developing world have a single dual cause: poverty linked with inequality. Working on eradication of the root cause would change our prospects in this field from a win/lose situation to a win/win situation.

ADDENDUM

ANNEX 1: List of participants of the expert meeting Extending the pipeline; towards a comprehensive and coordinated EU approach to Poverty Related Diseases, *Brussels, 10 April 2008*

DG Development		
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ANNEX 2: Program of the expert meeting

Extending the pipeline; towards a comprehensive and coordinated EU approach to Poverty Related Diseases, *Brussels, Hilton City Hotel, April 10 2008*

Day's Chairman: Jan Staman, director Rathenau Institute

Welcome with coffee and tea	8.30-9.00
Opening by chairman Wim van Velzen	9.00-9.05
Introduction of all participants	9.05-9.15
Part one: Introduction of the extended pipeline	
The extended pipeline— toward a comprehensive and coordinated European approach to Poverty Related Diseases Dr. Ellen ter Gast, Rathenau Institute	9.15-9.25
The EU programme for Action from the extended pipeline perspective	
a.) DG Research, Ole Olesen: Filling the pipeline	9.25 - 9.45
b.) EDCTP, Charles Mgone: Developing medicines and vaccines (phase 2 & 3)	9.45 -10.05
c.) Response by Stuart Blume, Innovia Foundation	10.05-10.15
Plenary discussion	10.15- 10.40
Coffee break	
Part two: Designing with the end-user in mind	
Selection of target disease: how can we avoid that some diseases become really neglected? **(**plenary discussion)	11.00-11.30
Focus of activities: what is the use of developing new drugs when health care systems are failing? **(**plenary discussion**)**	11:30-12:00
Designing drugs for developing countries: a problem of translation towards the end user? **(**plenary discussion**)**	12.00-12.30
Lunch	12.30-13.30

Part three: Coordinating with the end-user in mind

Coordination of activities: a leading role for TDR?	13.30-13:50
Introductory talk by Hans Remme (TDR)	
Plenary discussion: Role of developing countries in view of the (extended) pipeline	13.50-14.15
Partnering with the industry: a policy reality gap?	14.15-14.35
Introductory talk by Guy Willis (IFPMA)	
Plenary discussion: what else or what more should the EU Programme for Action do?	14.35-15.00
Tea break	15.00-15.15

Part four: SWOT analysis of EU Policy and practices 15.15-16.45

Strengths	**Weaknesses**
Opportunities	**Threats**

Closing remarks	16.45-17:00
Drinks	17:00-17.30

ANNEX 3: Report on the Expert meeting

Extending the Pipeline; towards a comprehensive and coordinated EU approach to Poverty Related Diseases, *Brussels, 10 April 2008*

Introduction

On April 10th 2008, a one-day expert meeting was organised by Rathenau Institute on the EU policy regarding PRDs in Brussels. During the expert meeting the essay 'Extending the pipeline—toward a comprehensive and coordinated EU approach to Poverty Related Neglected Diseases' (part one of this report) was discussed with a number of experts (see Annex 1 for the list of participants).

In the following an account of the day's proceeding is given by arranging topics thematically rather than chronologically. The meeting's programme is attached as Annex 2.

In his opening address, Rathenau Board Chairman Wim van Velzen welcomes this query of the simplistic pipeline model. He warns, however, that only actionable recommendations will do for Members of the EU Parliament to heed the meeting's outcome. Cautioning against 'brilliant academic reports', he calls for a judicious blend of scientific and practical notions as the ingredients for a 'top paper'. Van Velzen also points out the (under-exploited) notion of complementarity between different actors, notably between DG DEV and DG Research, highlighted in his evaluation of the European & Developing Countries Clinical Trials Partnership (EDCTP)[8]. It is also possible that the pipeline extension, appealing as it is, proves an over-simplification for the complex reality of today's scenario of R&D on Poverty Related Diseases.

1) The extended pipeline

The aim of the expert meeting is to gain further insight in the question to what extent the

European Union is geared to draw lessons from current notions on the social, political, technical and economic obstacles in combating Poverty Related Diseases (PRD)[9], and how the EU should respond to these lessons in its future policy.

In short, the meeting is intended to constitute a collaborative learning process, of experts with and amongst each other. The objective is to come up with policy recommendations to the European Parliament on EU policy on PRDs, specifically with regard to R&D. As a means to reach that goal, it is collectively investigated whether the well-known concept of the drug development pipeline concept can usefully be extended. That is to say, it is explored whether an extension of the framework used in thinking about drug development (for PRDs) will enhance its usefulness, and help sort out some of the problems identified.

The classical pipeline is summarized below, with the proposed extended pipeline beneath it.

[8] http://www.edctp.org/fileadmin/documents/Final_IER_report.pdf

[9] The acronym PRD is used throughout this report, to denote Poverty Related Diseases; R&D for these diseases may or not be 'neglected' as well.

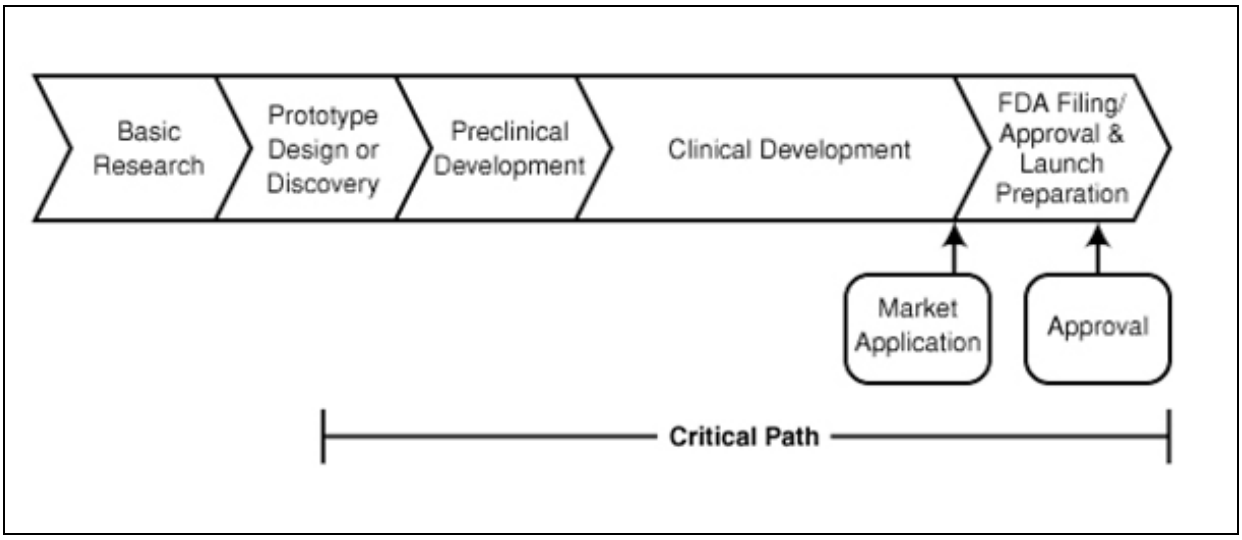


Figure 1 Classical Drug development pipeline

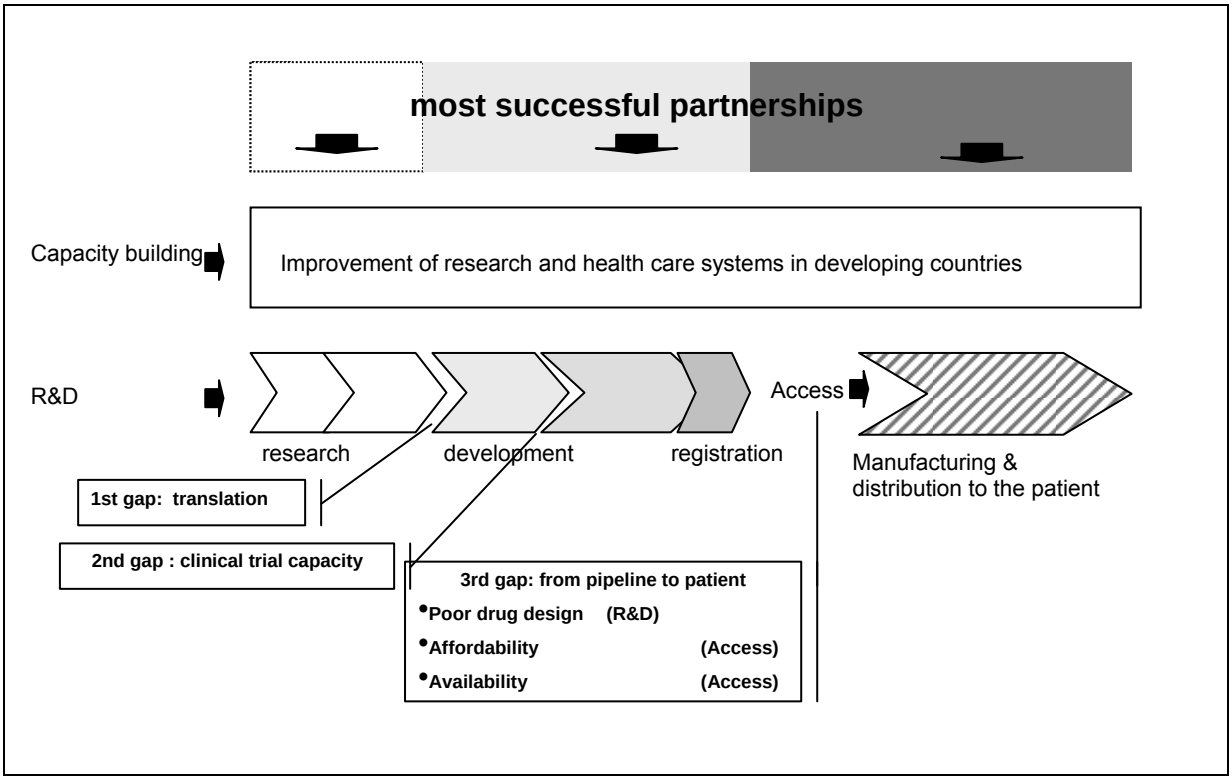


Figure 2 Extended pipeline

Noteworthy are the gaps the extended pipeline reveals. Questions on the extended pipeline are self-evident (Ellen ter Gast, Rathenau Institute): Is this extended pipeline helpful? Is the number and location of the gaps realistic? What are the main obstacles in the pipeline?

Assuming the concept is helpful and there is agreement on the pipeline's gaps, a next set of questions arises: How can the obstacles best be overcome? What are the critical success factors to make this pipeline flow? What criteria can be derived when it comes to deciding on how to feed the pipeline? What parties should be involved in the different phases of the extended pipeline? It is on such questions that the various speakers of the day, and the plenary discussions, will focus.

Critical in the discussions is the concept of feedback loops: does the reality 'at the end of the pipeline' sufficiently inform the actions taken throughout the flow through the pipeline—or even *before* the pipeline's point of entry? (See the figure 3 below from the presentation of Ellen ter Gast)

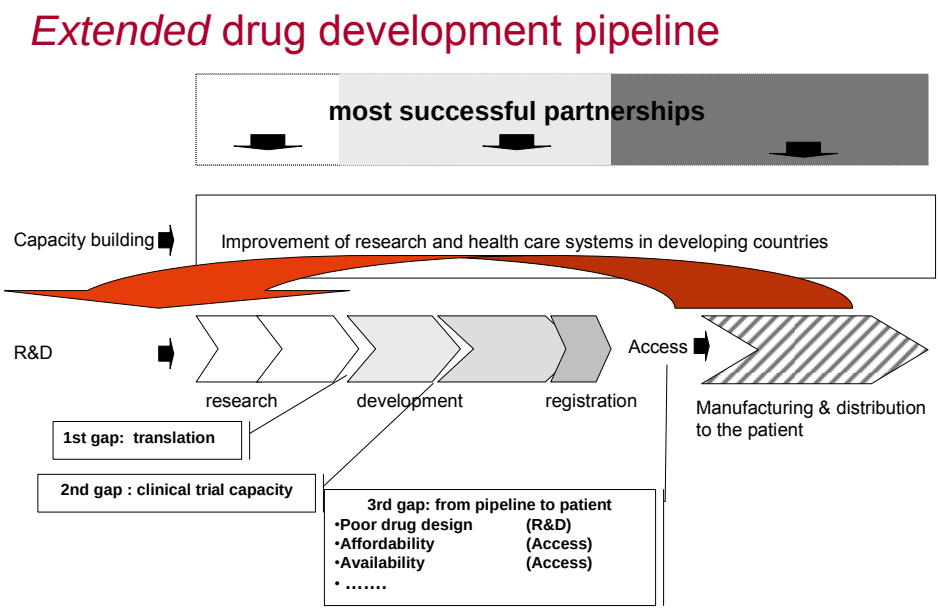


Figure 3 Feedback loops in the extended drug development pipeline (presentation Ellen ter Gast)

2) Clarifications

During the day the existence of gaps in the pipeline is emphatically confirmed. However, the need for clarification arises time and again, not so much on the nature of the gaps but on the extent to which gaps will be part of the agenda of the day. For instance: *Is resistance against drugs part of the agenda?* asks Steven Smits (Malaria no More). That is: should the feedback loop at the end start even further down the line? *And are we talking drugs only, or also vaccines and diagnostics?* queries Andreas Holtel of DG Research. The answer is affirmative.

Various participants insist on a R&D focus, leaving other considerations, notably of health systems strengthening, aside. Others point out that 'proper use' of a drug is a huge problem that cannot be ignored and should be taken into account in any attempt at a coordinated and coherent fight against PRDs. Parallels are drawn with the Western world, for example with regard to desirables for Alzheimer medication. Ellen ter Gast (Rathenau Institute) emphasizes that even for "R&D sec" the bigger picture must always inform one's strategy, the two cannot be separated.

Stuart Blume (Innovia) queries the concept of 'poverty related diseases'. Helpful as this notion may be for a policy-maker it is overly suggestive. The suggestion that "global human health" can be furthered by the development of (new) drugs for specific diseases distracts from what really matters: poverty. He suggests to speak of "poverty disease" rather than poverty related diseases. In order to illustrate this he points out how diseases differ from place to place: measles still is a problem in one setting and no longer in another. It follows that technologies have 'contingent utility' only. A universal rule is that it requires understanding the history of past problems in order to make headway in current ones.

With some talking back and forth it appears that there is agreement on the need to have 'the end of the pipeline' inform its beginning. For this the notion 'end-user' is helpful. Controversy remains on how to translate this into prescriptive dos and don'ts.

It appears that different participants have different expectations of the day but that nonetheless all are united in a common interest on the topic at hand. Staff of DG Research emphasise their hope for practical suggestions, within the boundaries of technology development in their niche in DG Research (i.e., Infectious Diseases).

3) Discussion: the pipeline as a metaphor

The presentations during the day demonstrate something that is perhaps self-evident: the nature of the pipeline is *intrinsically* intractable because of the given fact that the flow through the pipeline, for any product at its entry, can not be foreseen. According to some, this means that taking into consideration end-users from the very point of feeding the pipeline can be premature and even wasteful. It is argued that only 'time can tell' whether a product has sufficient qualities to enter the next phase and the next and in the end can do what it is supposed to do: provide a cure, diagnosis or prevention, with sufficient precision and without unwanted side-effects. A large but unknown proportion of hopefuls thus drop out of the pipeline all along its course. This is particularly painful—and costly—where this happens towards the end, as Guy Willis emphasizes in his presentation [See figure 4].

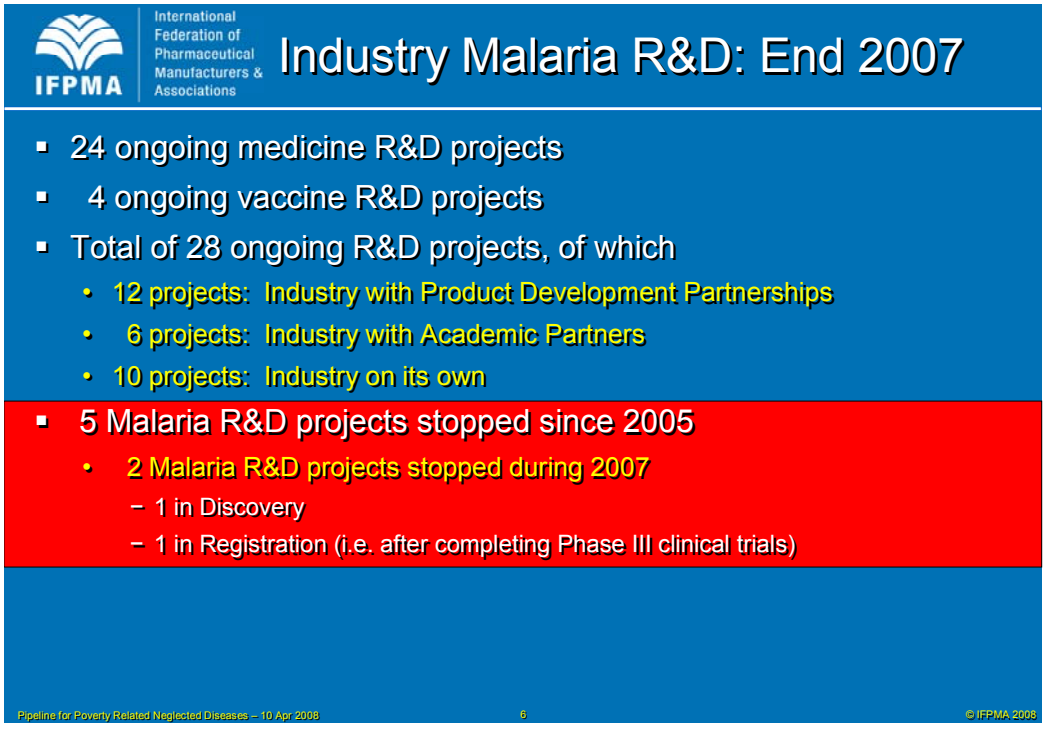


Figure 4 The flow through the Malaria Drugs R&D pipeline (presentation Guy Willis)

A variety of metaphors of the drug development pipeline thus draw smiles of recognition: the pipeline as a maze, riddled with loops and dead-ends (Charles Mgone, EDCTP); or as an irrigation plot (Stuart Blume, Innovia); or even as a pipeline made out of different materials. Given all this, one speaker calls the R&D path a 'gamble', necessitating a particularly courageous and tenacious brand of players.

> ***"The "pipeline" is a helpful image for explaining the drug development process. However, […] it risks conveying the impression that PRDs can be addressed simply by developing and supplying the necessary drugs."***

According to Charles Mgone there is a danger that the parts of the pipeline may not fit properly with each other or do not align well since there are different players working at different parts and laying different sections of the pipeline. This calls for the coordination and close collaboration of the different players.

The slides shown by Ole Olesen (DG Research) demonstrate activities along the different parts of the pipeline in the EU's FP6: R&D for PRDs has been allocated €458 million, of which €86 million (19%) for discovery; €134 million (34%) for transitional R&D; and €237 million (52%) for clinical trials and capacity - the latter exclusively through EDCTP (See Table 1).

Table 1: Pipeline approach for PRD, in EU FP6 [OO5]

Discovery (19%)	**Translational (34%)**	**Clinical (52%)**
	Preclinical research up to early clinical testing	Programme funding to phase II and III clinical trials in Sub-Saharan Africa
Small consortia • 1-3 m€ • average 2-3 years FP6: Approx. 70 projects	Large consortia, of 10-30 partners • 5-20 m€ • average 4-5 years FP6: 10 projects	Clinical Trials • 200 m€ • average 5-7 years FP6: EDCTP programme

The table illustrates that the EU FP6 cuts the pipeline in segments which are more or less independent from each other, also institutionally.

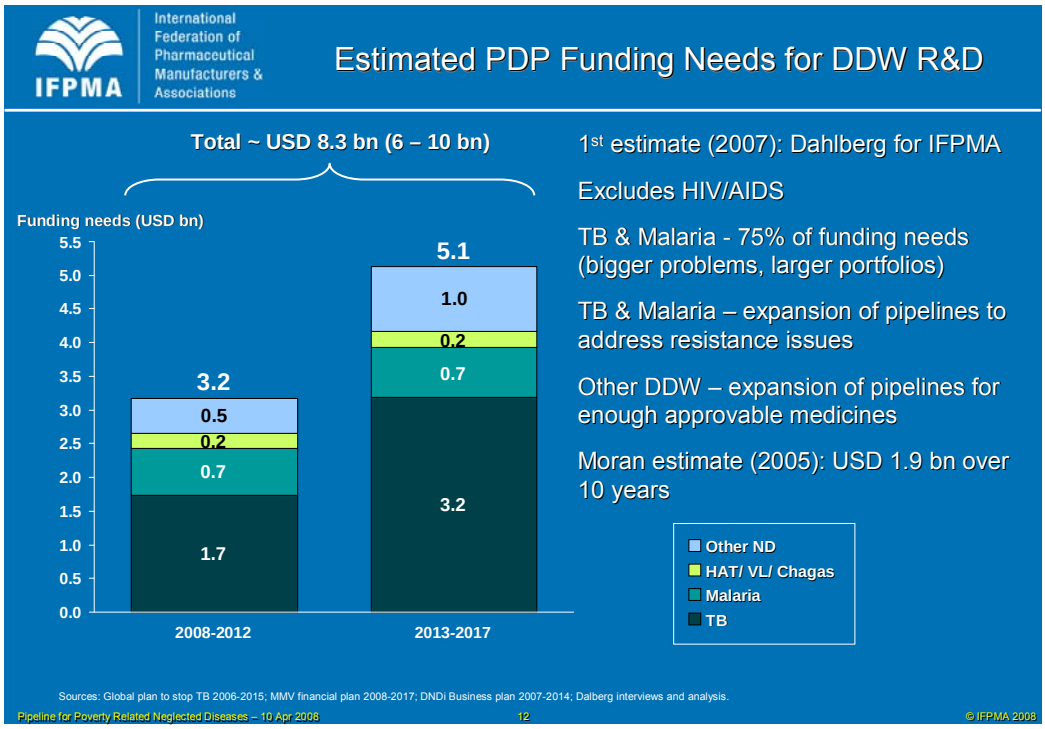
Another point of critique is raised by Guy Willis, who claims that the

> *"pipeline" is a helpful image for explaining the drug development process. However, it is much less suitable for explaining the much broader topic of addressing poverty related diseases[10]. In particular, it risks conveying the impression that PRDs can be addressed simply by developing and supplying the necessary drugs. This is dangerously misleading. Even in the most developed countries, drugs account for no more than 20% of total health expenditure – much more is spent on health workers, hospitals, clinics, laboratories, etc. Indeed, in many developing countries, the lack of adequately trained health workers and infastructure is actually a severe constraint on effective use of medicines. It is no coincidence that the GAVI Alliance and the Global Fund to fight AIDS, TB and malaria are allocating an increasing amount of their grant funding, not for medicines, but to reinforce beneficiary countries' health care systems, while more than half of the industry-backed partnership programs for the developing world involve some form of capacity building, providing training or strengthening infrastructure.*

4) Neglecting Diseases?

> ***"The public pie is as big as it is; giving a larger share to one disease inevitably means cutting down on another one. You could say that the funding of the one disease is thereby the cause of neglect of another"***

Another issue that is emphasised during the day is the paucity of resources dedicated to R&D on PRDs, as compared to the absolute needs. This is pointed out especially by Guy Willis (IFPMA) in his presentation (see Table 2). The PDP funding needs for the neglected diseases (here: excluding HIV/AIDS) is estimated at USD 3.2 bn for the period 2008-2012 (figure 5).



[10] The following comment was sent after the expert meeting and communicated via email.

Figure 5 Estimated PDP Funding Needs for Diseases of the Developing World (DDW) R&D. (presentation Guy Willis)

In comparison: the EU FP6 spent on HIV/AIDS, TB & Malaria was USD 0.5 bn for the period 2002-06 (See figure 6) .

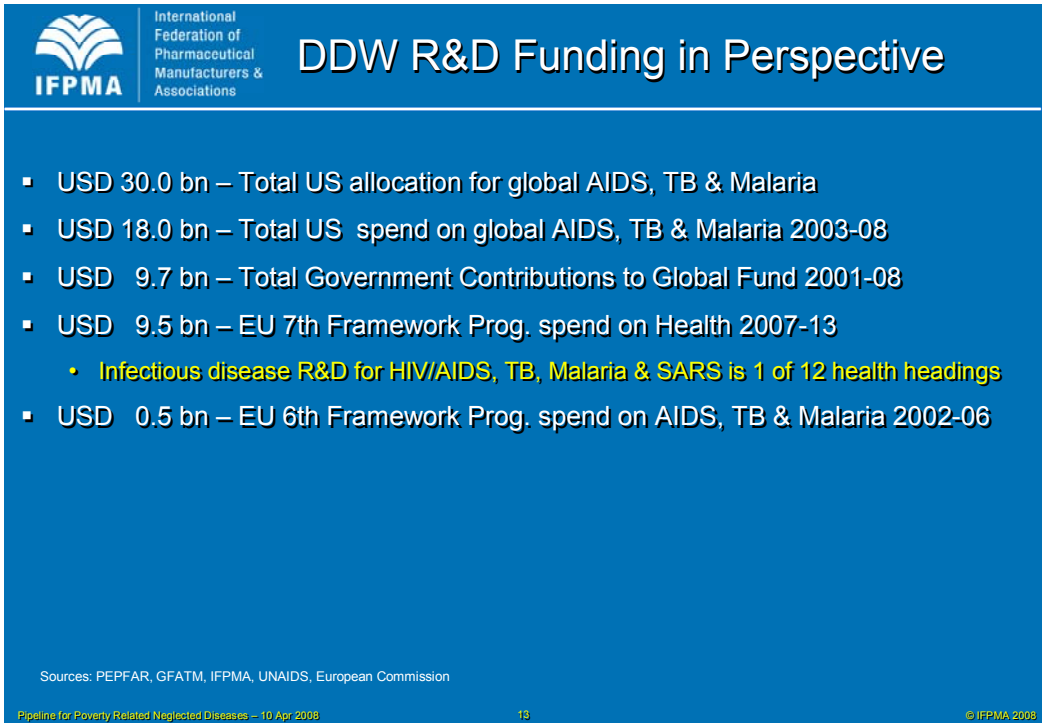


Figure 6 Diseases of the Developing Wolrd (DDW) R&D Funding in Perspective (presentation Guy Willis)

This forces us to consider in what directions the pipeline should or should not be extended—e.g., do not expand geographical focus, and carefully think about which diseases to target. As Ole Olesen from DG Research emphasises, *'The public pie is as big as it is; giving a larger share to one disease inevitably means cutting down on another one. You could say that the funding of the one disease is thereby the cause of neglect of another'.*

Table 2: What's being done?* [GW3][11]

Disease	DALYs (mio/yr)	Current Medicine?	Industry R&D projects*	Non-Industry R&D projects
HIV / AIDS	84.4	Yes	92	?
Malaria	46.4	Yes	28	11
Tuberculosis	34.7	Yes	22	32
Lymfatic Filariasis	5.7	Yes	0	?
Leishmaniasis	2.1	Inadequate	1	11
Schistosomiasis	1.7	Yes	0	?
H. A. Trypanosomis	1.5	Inadequate	1	15
Chagas disease	0.6	Inadequate	0	5
Dengue	0.6	No	5	?
Onchocerciasis	0.4	Yes	1	0
Leprosy	0.2	Yes	0	0
Helminths	2.9	Yes	?	?

* Sources: DALYs – WHO / Current Medicines – IFPMA, PhRMA / R&D - IFPMA 2007, PhRMA 2006, Moran et al: New Landscape 2005, TB Alliance 2007)

5) Lost in translation—or how to reach the end of the pipeline?

Thomas Teuscher of Roll Back Malaria points out the pipeline's length in terms of time, thus focusing attention on the *future* dimension which must be heeded for any action in the present: products that are in the pipeline today will come out of it in five or more years from now. Hence *ideally* we know the needs of 2015 and beyond, but *actually* we of course don't. Therefore the best we can do is keep being alert – *articulated*, he calls it – on the pipeline's environment, how this changes continuously, and what this means for the approach taken. For malaria Teuscher warns against an overly narrow focus, and pleads for a vision of incremental approaches – not *either* insecticides *or* bednets *or* ACT *or* improved tests *in isolation*, but all of them *together* do the trick. Opting for (overly) simple solutions is a trap. As another participant puts it: *'Beware of fig leaves'*.

> ***"Organisations such as MMV know perfectly well what the practical requirements are at the end of the pipeline"***

[11] Please note that this table is presented by Guy Willis from the IFPMA. According to Health Action International this table does not give a correct en complete oversight of 'What's being done'. Since it neglects many public projects and does not give a transparent indication of the sources of funding for the research. '*Publicly funded research plays a key role in the development of new medicines. Worldwide about 50% of R&D spending is public money (Global Forum for Health Research: Monitoring Financial Flows for Health Research 2006).*
For most of the PDP efforts the funding of industry is only a small part of the funding. As Mary Moran shows in her report (M. Moran et al., New Landscape, 2005), only about 2% of the funding for PDPs comes from the industry. Data published bz IFPMA and PhRMA is listing such PDPs as "industry projects". Therefor such data is biased and should not be used without critical discussion.
In some areas as HIV vaccine research, the percentage of public funding is even higher." (HAI email communication)

Remarkably, one notion that is prominent in the Rathenau essay appears to have lost its poignancy[12], even though it is repeatedly emphasized in recent literature:

> *"[..] many products that have successfully completed the R&D process, have failed to achieve their full potential impact because of implementation problems that impeded access"* (TDR 2007 p.12).
>
> And:
>
> *"One of the most neglected research areas is the development, evaluation and improvement of new interventions and intervention strategies in real life settings and within a public health context. This research is critical, and provides disease endemic countries with the evidence they need to make informed health policy decisions on which products to use, how to use them, when to use them and how to optimize their public health utility"* (ibid. p. 11).

Guy Willis (IFPMA) calls the above translational concern 'a red herring', since *'organisations such as MMV know perfectly well what the practical requirements are at the end of the pipeline'*. It appears indeed that the relatively new Product Development Partnerships (PDPs) such as MMV are well positioned to make this particular difference, as they keep a clear eye on tangible results for particular ailments, while minimising attention on contextual issues that distract from their main aim. It is thus not necessarily so that PDPs limit themselves to product development and do not heed the system in which the product lands. Rather, they act as the situation requires.

As Jennifer Katz from DNDi puts it: 'I*n DRC and Angola we have trials running on sleeping sickness. There is no way for our agenda to work if we don't invest in the sites and work from local realities.'* Jean-Louis Excler from IAVI qualifies this: IAVI trials likewise involve local health systems, if only to the extent necessary to guarantee quality care (medical support; referrals) for the local population taking part in the trial. He adds, though, that IAVI as well is at a loss on what to do in those cases '*where we bring the cherry on top of the cake and yet the cake itself is missing.*'

According to Guy Willis '*companies also have a fairly clear idea about the characteristics which make for effective medicines for resource-constrained environments. The issue is less one of awareness of developing countries specific requirements and more one of the extra demands this makes of researchers. It is difficult enough to find a compound that is safe, well-tolerated and effective for a particular indication. Making it in a form which is easier to administer, with longer shelf life, and simpler to transport and stock poses additional challenges which need more time and money to address.'*

[12] During the expert meeting there was no dissenting opinion about this subject. However in email communication afterwards HAI explicitly emphasised that this issue did not loose its poignancy and that the contributions of the group on this issue might not reflect the global consensus on this. "*This issue has already been extensively debated in the WHO by the international Commission on Intellectual Property, Innovation and Public Health, with the results being published 2006 in the CIPIH report. Currently these issues are being discussed at intergovernmental negotiations at the WHO in Geneva at the International Working Group on Public Health, Innovation and Intellectual Property. Access is indeed a very acknowledged problem, and capacity building in developing countries is seen as a key objective because of this. Also, the lack of needs driven health research instead of, or complementing, market driven research for diseases affecting developing countries is a basic recommendation of the CIPIH report."*(HAI email communication)

> ***"Increasing the competitiveness of European health-related industries and businesses is the EU program's first aim."***

However, it is unclear to what extent EU policy can respond to this, since EU policy on such issues is determined by the nature of the larger EU programme of which the R&D for PRDs is only a part. That is to say, the room for manoeuvre in EU policy on R&D for PRDs is constrained by the programme's main aim of increasing the competitiveness of European health-related industries and businesses. As Ole Olesen from DG Research states:'*This is our program's first aim and it is the same for all EU commissioned R&D, for all sectors, including, for example, space research.'* To put it differently: increasing the competitiveness of European health-related industries and businesses is a non-negotiable filter for all R&D calls, including those concerning PRDs. This will undoubtedly be reflected in the type of R&D projects the EU is in a position to fund.

6) Partnerships as prerequisite to a successful pipeline

Other organisations than the EU have more freedom to define their strategies primarily or even exclusively on the basis of criteria having to do with alleviation of (perceived) health needs of Third World end-users. Yet also those organisations need to remain alert on how to optimize their work so as to maximally provide added value. This includes making sure that one's actions are complementary to those of other organisations.

> ***Finding 'the right partners' is generally acknowledged to rank among the biggest challenges, for any result-oriented R&D effort on PRDs.***

The big difference with the EU is that such organisations can choose their partners on merit, and can think of all sorts of ways to self-organize the pipeline's flow and optimize the outcome. They can also *foresee* obstacles and extend the pipeline as far as is needed, for any particular product. Anna Wang: *'MMV is taking into account "the third D" of delivery. There are no actors to whom you can hand over the baton once you have developed your product. You need partnerships there. MMV is asking what it can do as a facilitator when it comes to access and delivery. How to get the drugs to the kiosk, not just to the clinic. Although MMV is an NGO, it works like industry. Access then also feeds in into our research. For example, we found fever reduction to be a desired quality so we put it in our malaria drugs.'*

Finding 'the right partners' is generally acknowledged to rank among the biggest challenges, for any result-oriented R&D effort on PRDs. This, as various PDP representatives gathered around the table mention, requires tailor-made partnerships, all along the pipeline, with the tailoring tuned both to the illness that is addressed and to the health care system shortcomings that may be expected as well as to a host of other factors. It follows that having the freedom to select the optimal partners is of paramount importance for successful R&D. 'We must find the science wherever it is', as Jean-Louis Excler puts is, while at the same time agreeing with Charles Mgone that Africa remains under-represented in the discovery segment of the pipeline.

7) Minding both the pipeline's gaps and its environment

As mentioned, the game of R&D for PRDs has the nature of a gamble. However, even though uncertainties are rife there are also knowns amidst the many unknowns. This is because patterns arise in the 'cumulative pipeline', with some gaps being more evident than others. Sometimes the gaps are given different names by the different actors dealing with them – see for example the difference between the images from the presentation of Ole Olesen [OO3, see figure 7] as compared to the presentation of Charles Mgone [CM3, see figure 8] .

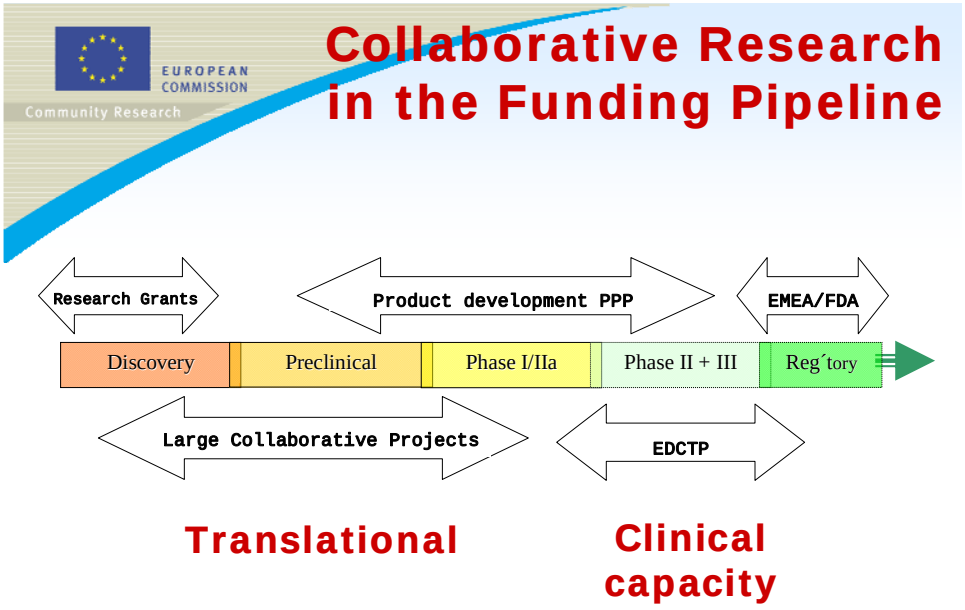


Figure 7, Collaborative Research in the Funding Pipeline (OO3, presentation Ole Olesen)

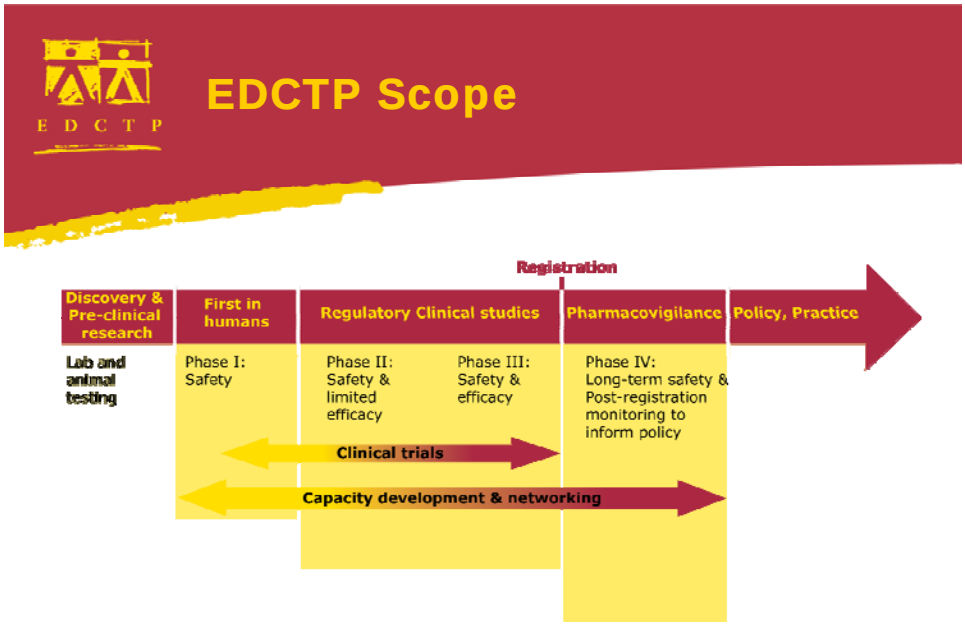


Figure 8, The scope of EDCTP (CM3, presentation Charles Mgone)

> ***"We have so many pipelines, and some may be heading in the wrong direction, or are not aligned with others."***

This applies to both gaps within the pipeline and to contextual concepts – where 'capacity building', 'knowledge management' and 'stewardship' may mean the same, or nearly so, as 'empowerment' and 'ownership'. The pipeline concept itself, however, proves robust and remains a visual help to situate the various shortcomings and the remedies proclaimed. Yet, as indicated above, the concept of a pipeline is but a tool and does not in itself provide a remedy for pertinent problems such as shortages of funds to address PRDs. In particular, the image of a *single* pipeline appears unsuitable when dealing with the issue of coordination. Dr Charles Mgone (NDCTP) has a way of saying this: *'We have so many pipelines, and some may be heading in the wrong direction, or are not aligned with others.'*

Given the multitude of pipelines, deciding on where to focus appears to be a risky endeavour. Choosing to invest in a particular pipeline almost necessarily entails that one leaves another gap for what it is. Moreover, such decisions seem nearly arbitrary, given that a rational argument can be made and evidence can be given to support almost any stand.

Guy Willis from IFPMA points out that some hard facts stand out and should be taken into account: when we look at the notorious TDR list of neglected diseases there are four of them – Leishmaniasis, Human African Trypanosomis, Chagas disease and Dengue - for which there currently is either no medicine at all or an inadequate one (see Table 2). Taking into account the EU's limited budget for PRDs – especially given the total needs – a strategic choice should be made for a limited domain in which the EU would then be an important player.

Staff of DG Research confirms that there is a constant risk of being drawn in all directions and thereby loose focus. An example would be expansion to continents other than Africa. Another example, already implemented in FP7, is the expansion to a less limited group of PRDs. Such dilemmas are also felt by the EDCTP, as there is a demand to extend the activities to Phase I through to IV clinical trials, to take up PRDs other than the Big Three, to add health services research, and to support country competence in pharmaco-vigilance (See figure 9 from the presentation of Charles Mgone).

Figure 9: Possible extension and broadening of the pipeline (presentation by Charles Mgone)

8) A pipeline surrounded by different actors—but who coordinates?

Given the changes in what already is a complex domain the necessity of coordination comes up time and again, and with different meanings. Although it is clear that there is urgent need for coordination of the numerous global activities in the field of PRDs, it remains unclear who should be responsible for it. Or, to put in the words of Ole Olesen, DG Research '*Everyone wants to coordinate, nobody wants to be coordinated.'* Hans Remme, WHO TDR, carefully avoids the suggestion that TDR could take the lead by being the central coordinator. TDR prefers the notions of stewardship and facilitator.

First and foremost there is a basic need for information. According to Hans Remme from the TDR, *'Nobody can see the whole picture anymore'*. More specifically, given the multitude of initiatives (Table 2 last two columns) it is increasingly important for all actors to be updated on what others do, and be prepared to make amendments in one's own program in response to developments in those of others. This concept of seeking to provide *added value* (responsiveness) is most outspoken in Hans Remme's presentation on TDR and how TDR hopes to live up to recommendations made in its recent external review[13].

> ***"Everyone wants to coordinate, nobody wants to be coordinated."***

At the same time there is agreement that staying abreast of all developments, including, of course, on epidemiological changes as they arise, is a tall order. As Stuart Blume remarks, *'We have an issue here on what kind of information ought to be an input; and how to bring the various institutions together; and who has the mandate to do this'*.

[13] http://www.who.int/tdr/publications/publications/pdf/10_year_vision.pdf

It is here that DG Research participants express self-criticism on their own institutional setting and internal arrangements which tend to make staff responsible for R&D on one specific disease without having an overview on the bigger picture and on new developments. This, they say, used to be different in the time of the EU Programme for Action which gave more room for joint strategising, for calling meetings and operationalising a proper strategy. Other participants mention that EU absence in the fora that matter is noteworthy. A related issue to the one discussed above, is that of the mechanism of calls for proposals, with (too) little room to include actors of choice and for making amendments en route. All in all the EU mechanism, in so far as PRDs R&D is concerned, is not conducive to responsiveness.

Several participants indicate that they keep having difficulties with the upfront requirement to work with European partners in the EU Framework Programme. As indicated above, PDPs operate in a result-oriented modality in which partners are selected for their specific added value, for R&D of a particular product. As Jennifer Katz (DNDi) puts it, '*Though we were pleased to see that calls under FP7 give a slightly wider focus to capacity building we keep having problems to balance this with the requirement of European competitiveness*'.

Charles Mgone relates that EDCTP has started a running inventory of all clinical trials, at present limited to trials in Africa, on HIV/AIDS, Tuberculosis and Malaria.[14] The reason, as he explains, is the need *'to know what is happening'*, but, just as importantly, *'to know what has been tried, but failed'*. The inventory is linked to the WHO registry.

A clear trend is the increased involvement of Third World countries, and in particular the *nature* of the involvement. EDCTP is aiming to use the clinical trials as an opportunity to ready host countries' capacity and even independence on regulatory issues and on being in charge of ethics reviews. TDR has moved all (6) Disease Reference Groups and (4) Thematic Reference Groups to the continent or region that is most pertinent, given the (group of) diseases or thematic issues which they address. All DRGs and TRGs have a global role; none of them is based in Europe or Northern America. Both TDR and EDCTP aim for a structured and progressive process towards ownership where it belongs. Examples are the South-South collaboration and principle of mentorship of EDCTP (See figure 10 below from the presentation of Charles Mgone). A TDR example is portrayed in a slide in the presentation of Hans Remme on progressive R&D leadership. Both EDCTP and TDR acknowledge that these are new initiatives, the results of which are yet to become evident.

[14] http://www.edctp.org/Clinical_Trials_Registry.145.0.html

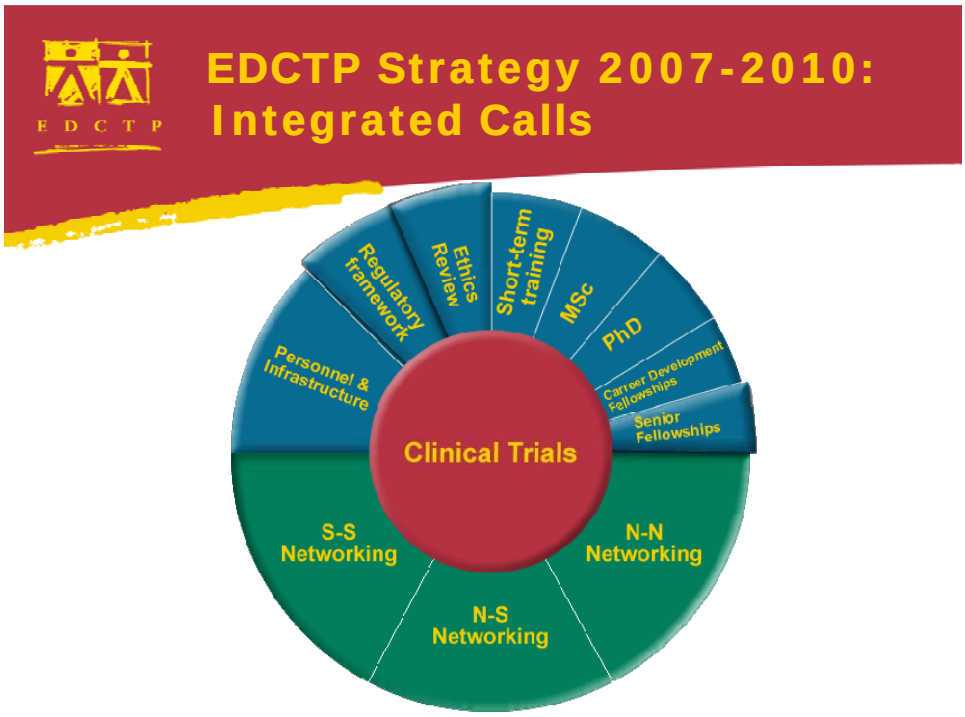


Figure 10 EDCTP Strategy 2007-2010 (presentation Charles Mgone)

9) SWOT analysis

At the end of the day the results of the day are summarised in a SWOT analysis. The SWOT is 'fed' by the facilitators' notes of the day's proceedings and edited and added on by participants of the meeting. The SWOT's focus, after some deliberation, is exclusively on the EU policies on PRDs, with emphasis on R&D regarding on Infectious Diseases. In the Table below the result of the SWOT can be found; readers please note that, to do justice to the concept of a SWOT, the entries are not edited. After the SWOT a few remarks are placed to put the SWOT in perspective and to highlight what is considered to be most important by the authors of this report. However, a few remarks in advance are also welcome.

At the expert meeting EU representatives of DG Development, DG Research and the EDCTP are present. Ole Olesen from DG Development and Charles Magone from EDCTP presented data on their respective projects. It stands out that much of this is new for many of the meeting's participants— hence the conclusion that the EU program on PRDs lacks visibility in the field. One consequence of this lack of visibility is that the SWOT analysis is based more on personal experience of the various participants in dealing with the EU, than on a thorough overall picture of its projects. For more detailed information on the EU projects, we refer to the attached presentations as well as COM (2001, 2003, 2004, 2005) as well as EC DG Research (2007).

Table 3: SWOT analysis of EU Policy and Practices regarding R&D of PRDs

Strengths and potential strengths	Weaknesses and potential to address them
• Funding of non-EU research needs • Funding as such • Focus on R&D, especially early stages • Coordinated programme for action on PRD; *strategy* • Esp. EDCTP: focus on Africa • Funding for support services • Focus on partnership building • EC money creating leverage for funding from EU member states (25%+)	• Lack of operationalisation of programme for action • Institutional set-up/ no managerial unit/ insufficient coherence • Lack of visibility, presence in global fora • Funding of *neglected* diseases • Impossible to be proactive • No attention for chronic conditions • Not necessarily science-driven (controversial) • Limited flexibility (e.g. requirements of 3 partners); bureaucracy • "One size fits all"-thinking
Opportunities and how to explore them	**Threats and who should signal them**
• Focus on delivery? • *Beyond* delivery: focus on *impact*? • Taking into account the needs of the end-user • Product Development Partnerships • Capitalize on funding • Setting priorities (seeking alternative answers to resistance) • More linkages with DG DEV • Linkages with TDR and… • Alternative means of funding from perspective of health development • Expansion to non-African countries (controversial) • Encourage biotech involvement and reaching out to them (strength?)	• Everybody wants to coordinate, but nobody wants to be coordinated. • Trade policy/considerations predominant and overruling research remit • Potentially conflicting objectives • Brain drain • *Internal* brain drain • Overruling national priorities

In general there is positive agreement about the fact that the EU spends part of its research funds on research on PRDs. The former presence of a concrete and coordinated programme for action is also considered to be one of the EU strengths. However, the programme for action has not been updated since 2005 and such a coherent programme for action is not part of the FP7.

A major threat to the effectiveness of the coherent programme for action is the absence of a supporting organisational structure. At present there seems to be little or no communication between different DGs about the EU action on PRDs as a comprehensive and coordinated whole.

Participation in PPPs and PDPs is mentioned as an opportunity, since it is generally agreed that presently such partnerships are most successful when it comes to targeting PRDs. It is mentioned several times that in order to be successful, EU R&D projects should partner with industry somewhere along the pipeline. Moreover, it is agreed– also by EU representatives – that, despite the EU's outspoken intention to work in partnership with PPPs and PDPs, their presence in such partnerships is negligible.

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