Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by Warren Kaplan, Ph.D., JD, MPH

Background Paper 1
Introduction

By Warren Kaplan, Ph.D., JD, MPH
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1. Introduction to the Project

*Priority Medicines for Europe and the World* was commissioned by the Dutch Government as president of the European Union (EU) in 2003. The Report identified a priority list of medicines for Europe and the rest of the world, taking into account Europe’s ageing population, the increasing burden of non-communicable illnesses in developing countries and diseases which persist in spite of the availability of effective treatments. The report looked at the gaps in research and innovation for these medicines and provides specific policy options on creating incentives and for closing those gaps.

The report identified gaps for diseases for which treatments do not exist, are inadequate, or are not reaching patients. Threats to public health such as antibacterial resistance or pandemic influenza, for which present treatments or preventive measures are unlikely to be effective in the future, were described. The report suggested that Europe can and should play a global leadership role in public health, as reflected by its history of social services provision and social safety nets for all citizens. The report maintained that where the market is strong and the problem is poor, understanding of the basic biology of the disease, inadequate investment in basic and translational research and in facilitating innovation by the pharmaceutical industry will be needed. Where the biology is well understood but the market is weak, public support for breaching the gap between basic and clinical research — possibly through public-private partnerships and other not-for-profit product development initiatives — was identified as the preferred solution. Where the biology is not well understood and there is also a weak market, then biological research can be supported while market incentives are created for the pharmaceutical industry, through reducing barriers to innovation and through improving reimbursement rewards.

1.1 Background to the Project Update

The 2004 Report was generally well received by most of the major stakeholders, including patients’ organizations, industry, governments and regulators. However, there was also some criticism. EURORDIS, the European alliance of rare disease patients’ organizations, had reservations about some aspects of the Report’s treatment of rare diseases. The International Alliance of Patients’ Organizations (IAPO) in Europe, although generally supportive, would have preferred the Report’s content to be have been written in a way that would be more accessible to patients, whom they consider to be critical in moving biomedical innovation forward.

**Pharmaceutical Forum and Initial Activity Leading to this Update**

The High Level Pharmaceutical Forum was set up in 2005 as a three-year process, in order to find relevant solutions to public health considerations regarding pharmaceuticals, while ensuring the competitiveness of the industry and the sustainability of the national health care systems. This high-level ministerial platform for discussion between Member States, EU institutions, industry, health care professionals, patients, and insurance funds focused its work on three main topics: information to patients on diseases and treatment options;
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pricing and reimbursement policy and relative effectiveness. See Appendix 1.1. The Forum is a follow-up to the High Level Group on Innovation and Provision of Medicines, called the “G-10 Initiative”. (See Background to Chapter 2 of 2004 Report and http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical-forum/g10_en.htm).

The last Ministerial meeting, on 2 October 2008, concluded this process by adopting the final report. See Updated Appendix 1.1a. It also included all technical documents and projects developed by the three working groups to support implementing actions addressed to the European Commission, Member States and interested stakeholders. The Pharmaceutical Forum led to a transparent exchange of views and the creation of European principles and methodologies on information to patients, pricing policy and comparative effectiveness.

The platform on access to medicines in Europe is one of the three work areas of the Process on Corporate Responsibility in the field of Pharmaceuticals. Relevant for present purposes, on 24 September 2010 the first meeting of the Steering Group of the platform on access to medicines in Europe (EC, Enterprise and Industry Directorate-DG) was held. The platform is part of the process on corporate responsibility in the field of pharmaceuticals.

The platform was to be composed of a Steering Group who would supervise five projects on access to orphan medicines and biosimilars, various capacity building, and governance initiatives. Further, a sixth project was proposed based on the original report Priority Medicines for Europe and the World, first commissioned by the Dutch Government during their Presidency in 2004. To quote from the minutes of the Steering Committee:

“The report Priority Medicines for Europe and the World …, commissioned by the Dutch Government during their Presidency in 2004, was referred to as a good starting point. This proposal received an important support by the Members as the projects identified primarily target the challenges of access. It appeared to the members that the innovation component of the triangle “Access-Innovation-financial sustainability” identified within the Pharmaceutical Forum … was less in the focus. It was agreed the need to explore how to include this proposal in the work of the platform and potentially as a specific task of the Steering Group”.

In May 2011, the Working Group on access to medicines of the European Commission, following a meeting held in April 2011 in Brussels, made a “… recommendation … to ask WHO to update Chapters 1-6 of the 2004 Priority Medicines report and to establish a working group to update Chapter 7 (cross-cutting themes) and Chapter 8 (new approaches to promoting innovation). “ The Working Group noted that an updated report “…should be published in 2014 for the 10th anniversary of its original publication.” See Updated Appendix 1.1b, Section 1(f), page 2.

The April 2011 Working Group meeting was held in Brussels with specific focus on the update to Priority Medicines for Europe and the World. See Appendix 1.1c. The meeting was hosted by the DG Enterprise and Industry. Representatives from Belgium, Hungary, Italy, the Netherlands, Norway, Portugal, Switzerland, and various organizations (EFPIA, EPF, EIP, EuropaBio, WHO, and DG Enterprise) were present. With regard to prioritization for innovative biomedical products, a number of themes were recurrent:

- How to find common language and common ground among stakeholders.
- How to integrate priorities in pricing and reimbursement procedures.
- How to measure innovation in fields as prevention, adherence, quality of life.
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- How to conciliate priorities of different stakeholders in order to achieve societal goals.
- How to conciliate the different time perspectives of stakeholders? (long research timelines and annual budgets).

The group agreed that the 2004 report continues to be relevant in its structure and methodology. The Working Group decided that the update should follow a dual approach (See Updated Background Chapter 4).

- Determine whether the therapeutic areas identified in the 2004 report still contain pharmaceutical “gaps”. Thus, data in chapters 1 to 6 should be updated.
- The sections of the original report on cross-cutting themes and new approaches to promoting innovation should be updated with a different methodology.

Specifically, certain cross-cutting themes may be important for all therapeutic areas in Chapters 1-6, namely patient adherence, prevention, organizational issues (health systems), delivery systems, patient group specific issues (children, women, elderly people) product stability, diagnostics and biomarkers, orphan drugs, safety, and quality of life.

With regard to approaches to promoting innovation, it was agreed that the update needs to assess achievements to date to identify the following areas:

- What has and has not been working.
- Ways of integrating priorities in the chain of product-development, from research to patient with special focus on the role of patients and payers.
- Possible common ground between private and public and to determine what can be done to reduce time to market for important innovations.

The results of this meeting were presented by Norway at the Steering Group on access to medicines in Europe (Budapest, 4 May 2012). A contract was issued to the WHO in September 2012 to manage the entire project and produce the updated Report in 2013.

European Framework Programmes: Overview of 7th Framework

In 2003, the Government of the Netherlands had requested WHO to identify “priority medicines” (defined below) for certain high-burden priority diseases with reference to opportunities afforded within the European Union (EU). Targeted research funding has been available since 1984 through the various European Framework Programmes (See Background Chapter 2). More recently, the EU has had opportunities for encouraging innovation through possibilities for supporting clinical trials, such as through the European Developing Countries Clinical Trial Partnership, and supporting product development through the European Investment Bank. At the time of the original Priority Medicines Project, targeted research funding was available through the EU 6th European Framework Programme, which included the development of effective interventions for diseases of poverty, such as HIV/AIDS, malaria, and tuberculosis.6

The Government of the Netherlands was interested in creating a public-health-based medicines development agenda, for support by the EU as part of the EU 7th Framework Programme for 2007–2013. To address populations in developing countries that also need “priority medicines”, the WHO was asked to also identify disease conditions for which there was a commonality of interest with the rest of the world.
Sephth Framework Programme (FP7)*

This Programme is the European Union’s main instrument for funding research in Europe between 2007 and 2013. It was launched with a total budget of about 55 billion Euros. The Seventh Framework Programme supports research in selected priority areas, such as health (€6 billion) and food, agriculture, and biotechnology (€2 billion) over the duration of FP7.

European-funded health research was focused on several key areas:

- **Biotechnology, generic tools, and medical technologies for human health consisting of:** high-throughput research; detection, diagnosis and monitoring; prediction of suitability, safety, and efficacy of therapies; and innovative therapeutic approaches and intervention.

- **Translating research for human health consisting of:** integration of biological data and processes; research on the brain and related diseases, human development and ageing; translational research in infectious diseases (HIV/AIDS, malaria, tuberculosis, SARS, avian influenza); translational research in major diseases: cancer, cardiovascular disease, diabetes/obesity, rare diseases, other chronic diseases including rheumatoid diseases, arthritis, and musculoskeletal diseases.

- **Optimising the delivery of healthcare to European citizens consisting of:** translation of clinical outcome into clinical practice; quality, efficiency and solidarity of health care systems including transitional health care systems and home care strategies; enhanced disease prevention and better use of medicines; and appropriate use of new health therapies and technologies.

A database search was performed and Table 1.1 below summarizes the total number of FP7 funded projects in the medical areas identified in the 2004 Priority Medicines Report. In particular, we note the presence of many project related to new diagnostics.
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Table 1.1.1: Total number of FP7 funded projects in the medical areas identified in the 2004 Priority Medicines Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Medical area</th>
<th>Total number of funded projects (using search engine on EU webpage)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of relevant projects</td>
</tr>
<tr>
<td>1</td>
<td>Antibacterial drug resistance</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Pandemic influenza</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Cardiovascular disease</td>
<td>118</td>
</tr>
<tr>
<td>4</td>
<td>Diabetes*</td>
<td>108</td>
</tr>
<tr>
<td>5</td>
<td>Cancer and Cancer Therapeutics*</td>
<td>478</td>
</tr>
<tr>
<td>6</td>
<td>Acute stroke</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>HIV/AIDS*</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>Tuberculosis</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>Neglected diseases*</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>Malaria*</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>Alzheimer’s disease</td>
<td>118</td>
</tr>
<tr>
<td>12</td>
<td>Osteoarthritis*</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>COPD*</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>Alcohol use disorders*</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>Depression in young people and elderly</td>
<td>32</td>
</tr>
<tr>
<td>16</td>
<td>Post partum hemorrhage*</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>Tobacco use</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>Obesity*</td>
<td>58</td>
</tr>
</tbody>
</table>


The search term used was “neglected disease”. Only three projects were found but this could be due to the fact that the search was not done using the names of neglected diseases.

NOTE: This search used two search engines. For both search engines, key words closely related to the priority diseases of Chapter 6. For some areas it is easy to match the key words with the diseases (“cancer”, “diabetes”, “obesity”, etc); however, for some others there are different terms which might limit a complete capture of all projects (e.g. for antibacterial resistance there are “antimicrobial resistance”, “antibiotics”, “resistance”, “antibacterial resistance” etc).

### Top Institute Pharma

The pharmaceutical “gaps” identified in the first Priority Medicines Report serve as the core research portfolio for the Netherland’s Top Institute Pharma. TI Pharma’s mission is to establish, support and manage public-private collaborations between academia and the (inter-) national pharmaceutical industry, in part to create cross-disciplinary research, within the framework of Priority Medicines Report, to improve the efficiency of the entire drug...
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development process as well as to educate and train biomedical scientists in groundbreaking, cross-disciplinary research, within the framework of Priority Medicines Project. See http://www.tipharma.com/about-our-institute/our-mission.html).

As of 2012, 60 research consortia have been formed, combining 31 universities, their affiliated medical centers and knowledge institutes and 48 industrial partners including global pharmaceutical companies and small and medium-sized enterprises (SMEs). Therapeutic areas based on the original Priority Medicines Report consist of (auto)-immune diseases, cardiovascular diseases, infectious diseases, and brain diseases.

The Executive Board of TI Pharma appointed an independent Mid-Term Review Committee to evaluate TI Pharma and the report was published January 2010. It is useful to quote at some length from the Report (page 17):

TI Pharma is well on its way towards meeting its objectives and fulfilling its success criteria. The Committee is of the opinion that TI Pharma … delivers “value for money” and is thus, relatively speaking, a low-cost investment. TI Pharma is a unique link between universities, research institutes and large and small (bio)pharmaceutical companies… The Committee is unanimous in its opinion that TI Pharma – as it is today, and with its current mission – must continue.”

The Innovative Medicines Initiative

The Innovative Medicines Initiative (IMI) was launched in 2008 as a large-scale public–private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). To fulfill its mission, the IMI implements R&D programs focused on developing new tools and methods for predicting drug safety and efficacy as well as for more efficient knowledge management. Furthermore, the IMI supports education and training projects on these topics. EFPIA pharmaceutical companies invest in the IMI in the form of in-kind contributions by committing internal human resources or providing access to datasets and infrastructure. This industry investment is matched by funds from the European Union; the funds support other consortium members, including academic teams, small and medium-sized enterprises (SMEs), patients’ organizations, regulatory agencies, and relevant not-for-profit institutions. The first three calls for proposals, launched by the IMI in 2008, 2009, and 2010, resulted in 30 projects. Altogether, the resulting 30 consortia involve 25 EFPIA companies, 350 academic institutions, 55 SMEs, 11 patients’ organizations, and 10 regulatory agencies; the projects have a total budget of around €2 billion. The Interim Report on the functioning of the IMI was uniformly positive. The authors formulated a series of recommendations for action and, significantly, stipulated which actor(s) should take responsibility for them.

Initiatives to combat antimicrobial resistance (AMR)

The original Report identified AMR as a priority condition requiring coordinated efforts (see Chapter 6.1). The problem of AMR has been known for many years and has been recognized by the WHO, the EC and the European Parliament. The Swedish government during their period as EU President were very active and convened a major meeting. Through resolutions passed by the World Health Assembly (WHA), WHO Member States have highlighted not only the public health threat of resistant organisms, but also the harm caused by misuse of
antimicrobials by patients, prescribers and medicine dispensers. Activities following publication of the 2004 Report are encapsulated in the following WHA Resolutions:

- WHA58.27 – Improving the containment of antimicrobial resistance, 25 May 2005 (see Appendix 1.2a).
- WHA60.16 – Progress in the rational use of medicines, 23 May 2007 (see Appendix 1.2b).
- WHA62.15 – Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, 22 May 2009 (see Appendix 1.2c).

Antimicrobial resistance is the subject of research funded under the FP7 and the IMI, and is also the subject of a Joint Programming Initiative (JPI), which aims to coordinate research activities among EU Member States (http://ec.europa.eu/research In early 2010 the JPI on Antimicrobial Resistance was proposed by Sweden and Italy.  

In late 2011, the EC put forth a five year Action Plan on anti-microbial resistance (AMR), which has been singled out by the European Commission as a major public health concern. One of these priorities is implemented through the IMI 6th Call on antimicrobial resistance which forms part of the 'Action plan against the rising threats from Antimicrobial Resistance’ adopted by the European. The 6th Call 2012 is a single theme, that of Combating Antibiotic Resistance: NewDrugs4BadBugs (ND4BB).

Horizon 2020 (Framework Programme 8)

“Horizon 2020” (H2020) is the follow-up to Framework Programme 7 and is the name of the EU’s new programme on innovation and research. The European Parliament and European science ministers will vote on the entire program in November 2012. It is intended to finance a major initiative running from 2014 to 2020 with an €80 billion budget. It will combine all research and innovation funding currently provided through the Framework Programmes for Research and Technical Development, the innovation related activities of the Competitiveness and Innovation Framework Programme (CIP) and the European Institute of Innovation and Technology (EIT). (See Updated Appendix 1.3 and other background documents at http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=h2020-documents).

The budget is for both research and innovation, with a respective allocation of €24.6 billion to support ‘excellent science’ and €17.9 billion for ‘industrial leadership’ in innovation. The programme is intended to provide funding during the entire “innovation cycle”, that is, from “idea to market.” (See http://www.nature.com.ezproxy.bu.edu/nmat/journal/v11/n6/full/nmat3353.html).

The other key objective of the programme is to support research excellence. A dedicated budget of €13.2 billion will be allocated to the European Research Council (ERC), which will see its funding increase by 77% compared with FP7.

Another objective of H2020 is to fund multidisciplinary solutions to address much larger societal challenges in health, food, energy, transport, climate, and security. (See Updated Background Chapter 2) The H2020 initiative is not restricted to biomedical innovation.
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1.2 Objective of the Original Priority Medicines Project and the Update

The objective of the original project, as described in the initial proposal (See Annexes to Section 2 of original report) is identical to the updated Project:

_to prepare a public-health-based medicines development agenda, for support by the EU in the immediate … and medium-term … future, and to develop a systematic methodology in this regard._

_Within the context of tackling preventive and therapeutic gaps for the citizens of Europe, special emphasis will be put on identifying those research needs which are also relevant for countries in economic transition (including several new EU members) and, if possible, also for developing countries – so that a maximum benefit may be derived from a “commonality of interest”. In addition, needs regarding better delivery mechanisms/formulations of existing preventive and therapeutic medicines, will be identified._

It is accepted that the resources available for developing and supplying medicines to respond to unmet medical needs is not infinite and that decisions will have to be made between competing priorities. The aging of the EU population, the impact of EU Enlargement, and the relatively less developed state of healthcare systems in the EU Accession countries still pose substantial challenges. This is especially so when the EU seeks to meet the dual goals of promoting equity in healthcare on one hand, and promoting innovation and sustaining the competitiveness of the pharmaceutical and biotechnology industries on the other. The need for new medicines and the maintenance of high standards of safety are unarguable and the present system has served both these objectives and avoided major public health disasters. These issues are still with us. This project is not about improving access to medicines through improving the efficiency of the health care delivery system.a It is restricted to investigating EU pharmaceutical innovation from a public health viewpoint.

1.3 Priority Setting (2004-2012)

It seems beyond question that for even the most developed countries, the demand for healthcare outweighs the supply of resources allocated to finance it. As a result, the ability of national policy makers to set priorities for their health care system or for new technologies within the health care system is most often conducted in the face of varying degrees of evidence about the safety, effectiveness, and appropriateness of particular interventions. Thus, priority setting is a real challenge for every health care system in the world. As yet, it is safe to say that there are no widely accepted models for legitimate and fair priority setting in health care.

There are many different approaches to priority setting and much recent literature in this regard since the 2004 Report and these are reviewed briefly here and more extensively in the

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a An example of a “health delivery gap” is the situation regarding epilepsy, where a variety of political, economic, social, and cultural factors result in a difference between the numbers of people with epilepsy and the numbers actually being treated. See the ILAE Commission Report, “The Treatment Gap in Epilepsy: The Current Situation and Ways Forward”, Epilepsia, 42: 136-149 (2001).
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Chapter 3 update and its corresponding Background Chapter (See updated Chapter 3 and accompanying documentation).

During the past two decades, various priority setting exercises have included the Commission on Health Research for Development,\(^\text{12}\) the World Development Report (1993),\(^\text{13}\) the Ad Hoc Committee on Health Research (1996),\(^\text{14}\) the WHO Advisory Committee on Health Research (1997),\(^\text{15}\) the Global Forum for Health Research (2000),\(^\text{16}\) the joint initiative of the UN Development Program/World Bank/World Health Organization—the Special Program on Research and Training in Tropical Diseases (TDR) (2002)\(^\text{17}\) and the joint WHO-IFPMA Roundtable (See Original Report Appendix 3.7). With the exception of the TDR initiative and the joint WHO-IFPMA Roundtable exercise, we note that much of this work has been directed to identifying “gaps” in existing healthcare delivery interventions, and not in identifying “gaps” in pharmaceutical R&D.

The majority of subsequent priority-setting exercises since the Priority Medicines Report (2004) have applied a broad definition of health research as an activity that is not limited to generating new knowledge, but also has a vision of implementation that should help to reduce present disease burden. It is important therefore, to make a distinction between developing priorities for health care using existing technology and medicines and developing priorities for funding biomedical research to develop new, improved technologies and medicines.

In 2005, the Child Health and Nutrition Research Initiative (CHNRI, www.chnri.org), an initiative of the Global Forum for Health Research, launched a project to develop a systematic method for setting priorities in health research investments and to apply it to global child health.\(^\text{18}\)

In 2007, discussions at the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) emphasized a need for the development of methodologies for identifying gaps in research on diseases that disproportionately affect developing countries (See Updated Appendix 1.4a Draft global strategy and plan of action on public health, innovation and intellectual property: Priority-setting models for research and development (A/PHI/IGWG/2/INF.DOC./1), 20 September 2007; Updated Appendix 1.4b Draft global strategy and plan of action on public health, innovation and intellectual property: Report by the Secretariat (A/PHI/IGWG/2/2), 31 July 2007; Updated Appendix 1.4c Draft global strategy and plan of action on public health, innovation and intellectual property: Progress to date in drafting groups A and B (A/PHI/IGWG/2/conf. Paper No.1 Rev 1), 14 December 2007).

A workshop on Priority Setting Methodologies in Health Research was held at the World Health Organization in Geneva, Switzerland from 10th -11th April 2008. The overall workshop objective was to develop practical proposals for user-friendly methodologies for priority setting in health research for application in developing countries. Specifically, the workshop (1) reviewed the main priority setting methodologies utilized to date; (2) reviewed and assessed case studies of priority setting in various countries and for various topic areas; and (3) developed a framework of guiding principles and a practical approach to priority setting by bringing together salient elements of existing methodologies (See Updated Background Chapter 3 and accompanying documentation).
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In 2010, the World Health Organization (WHO) formulated their own literature review and an analysis of health research priority setting exercises that were organized or coordinated by the WHO since 2005. The authors proposed a checklist for health research priority setting that allows for informed choices on different approaches and outlines nine common themes of good practice (See updated Background Chapter 3 and accompanying documentation).

Several recent reviews point to the increasing awareness of priority-setting in health systems research. One recent review identified eighteen priority-setting studies. Ten of these studies prioritized existing interventions across the healthcare system, four studies across several disease areas, and four studies concentrated on particular disease areas (See Updated Background Chapter 3 and accompanying documentation).

Another review shows that the CHNRI methodology cited above has recently been used by several different groups to set health research priorities at the highest international level. For instance, the CHNRI method was recently implemented in South Africa. There are several other tools for setting research priorities at the national level, which were reviewed and evaluated by Tomlinson et al.

Other tools and processes have been dominant at the national level. The Council on Health Research for Development’s approach (COHRED) has been implemented in Brazil, Cameroon, Peru, and the Philippines; the Essential National Health Research (ENHR) approach in Cameroon and South Africa; and the Combined Approach Matrix (CAM) in Malaysia, Pakistan, and Argentina.

1.4 Burden of Disease, the Epidemiological Transition and the Commonality of interest

This project focuses on the requirements of different populations, all of whom are undergoing important social, demographic and epidemiological changes. Europe encompasses the twenty seven countries of the European Union, all of which are showing a rapidly aging population. See Updated Background Chapter 5. The “world” encompasses the population of the earth, including the twenty seven countries of the European Union. Many parts of this population outside the EU are particularly influenced by the large numbers of people who are undergoing their own epidemiologic and demographic transitions. This means that their healthcare systems are faced with aging populations and ever-increasing chronic non communicable diseases (NCDs) associated with life style and economic changes.

Various measures of measuring disease burden have been developed. We use in this Report the concept of DALYs as an integrated measure of mortality and disability. The indicator combines mortality and morbidity in a single measure. One DALY can be thought of as one lost year of ‘healthy’ life and the burden of disease as a measurement of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability. In brief, DALYs are a way of aggregating the number of life years lost by sufferers from each disease with the amount of disability suffered while they are still alive. These two amounts are combined in a complex manner to give the overall burden of that disease. See Background Paper Chapters 4 and 5. Mortality is also used here as a measure of burden of disease as this is easy to understand. However, this measure is not able to reflect
the burden of pain and suffering experienced by patients with chronic diseases such as osteoarthritis.

We live in a world where a commonality of interests means that the vast majority of chronic disease conditions affecting the EU such as cancers, heart and cerebrovascular disease as well as osteoarthritis and Alzheimer’s disease will also be occurring in the “developing” world in the future. In addition, large portions of the world’s poorest population also face the onslaught of AIDS combined with neglected diseases such as malaria, trypanosomiasis and tuberculosis in a double or triple burden of disease.

1.5 Priority Medicines and Pharmaceutical Gaps

In May 2004, ten countries joined the European Union (EU) and some of these countries had unique public health issues. For a number of diseases that affect all members of the EU, no effective and safe medicinal treatments are yet available (e.g. Alzheimer disease and several cancers). For some diseases, potentially large markets exist for medicines and associated pharmaceutical research is likely to be intensive for certain therapeutic classes. For other categories of medicines (e.g. for cystic fibrosis), the number of patients is low or the market-driven pharmaceutical industry has failed to pursue R&D (e.g. new medicines for tuberculosis). There are now 27 member countries in the EU and after May 2004 Bulgaria and Romania gained entrance in 2007.

For a given disease condition, we can define "priority medicines" in several ways:

1. Priority medicines are essential medicines which should be developed to treat conditions where few, or none, effective treatments exist. These are medicines that would fill pharmaceutical “gaps” (as defined below) and would be useful in Europe and anywhere in the world where the diseases exist that need effective treatments.

2. We further define "priority medicines" as being those essential medicines that have not yet been developed for conditions that will be important public health concerns in Europe and the rest of the world.

3. "Priority" medicines are also those medicines needed for neglected patient groups (patients having "orphan" diseases, the elderly, children, and women: Updated Background Chapters 7.5, 7.2, 7.3 and 7.4, respectively) and the so-called "neglected" diseases of primarily tropical origin. See Background Chapter 6.9.

“Priority medicines” are designed to fill pharmaceutical “gaps”. The project is focused on diseases for which treatments do not exist or are inadequate, and threats such as antibacterial resistance or pandemic influenza, for which present treatments or preventive measures are unlikely to be effective in the future. In addition, the project addresses obstacles where effective medicines could be better delivered to the patient. We have chosen to emphasize certain fixed dose combination medicines and heat stable formulations as worthy of further research and development. Finally, this project looks at particular groups such as children, women, and the elderly who have frequently been ignored in the scientific or drug development process.

The 2013 Priority Medicines Project continues to identify pharmaceutical gaps and to identify areas for improved delivery mechanisms or better formulations of existing preventive and therapeutic medicines (e.g. formulations for children, fixed-dose combinations (FDCs) or heat-stable formulations).
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Although the 2013 Report addresses some high-burden diseases that are largely preventable, such as lung cancer, chronic obstructive pulmonary disease (COPD), obesity, alcohol related diseases and tobacco smoking and Type 2 diabetes, it should be underlined that, with rare exceptions, any new treatment is unlikely to be a “magic bullet” and that health promotion and disease prevention (not considered in the present Report) must remain very high priorities.

It is encouraging to note that since 2004 two major pharmaceutical gaps identified in the original Priority Medicines Report have been addressed. The first of these is the introduction of imatanib for the treatment of chronic myelogenous leukemia illustrated in the Box 1.1 at the end of this Chapter, and the second is the use of antibiotics to treat the disabling condition of Buruli ulcer, which was being treated primarily with wide surgical excision. (See discussion of H2 antagonists and ulcer surgery in Annex to Chapter 1 of the original Report). Recent studies have confirmed the efficacy of antibiotics in treatment 22, 23 (see also Chapter 6.9).

1.6 Public Health Perspective

This project uses a public health perspective when addressing "pharmaceutical gaps." This involves considering the greatest good for the greatest number, the value of promoting healthy behavior, prevention where possible, and ensuring that access is assured to all who would benefit. We do address some diseases having a high burden, such as lung cancer and chronic obstructive pulmonary disease (COPD) where pharmaceutical gaps exist in spite of the fact that these conditions are in principle preventable. Health promotion, prevention and ensuring access will remain very high priorities for the future, although this report will focus on pharmaceutical interventions. From a public health perspective, a pharmaceutical “gap” can be filled with an innovative medicine having a new mode of action, an existing medicine with a less harmful side effect profile, or a medicine (whether or not innovative) that can be delivered to the patient with a better delivery system (e.g. fixed dose combinations or heat stable formulations).

1.7 Conceptual Framework

We conceptualize the fact that no effective and safe medicinal curative treatment are yet available for certain conditions as the existence of an obvious “pharmaceutical gap” between burden of disease and clinically effective medicine. Funding for pharmaceutical research, in relation to preventive and curative gaps with considerable public health impact, should therefore be considered. Figure 1.1 (adapted from Figure 1.1 of the Combined Approach Matrix developed by the Global Forum for Health Research, See Original Report Appendix 3.6) has a vertical axis that is the combined efficacy of all pharmaceutical interventions used for a particular disease condition, whether cost effective or not. The horizontal axis represents the proportion of the total population with that condition that is covered by the available mix of interventions. Delineations on the horizontal axis are arbitrary levels of population coverage. One can attempt to identify “pharmaceutical gap” labelled as: BOX 4 - where there is not yet any intervention at all (whether or not cost effective), or BOX 3 - where an existing intervention can be improved in either or both a cost-effectiveness and/or therapeutic sense. For instance, eliminating a situation where there is not yet any intervention for a disease with a large global burden would be treating and diagnosing Alzheimer disease. Eliminating a “gap” where existing interventions can be improved might
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happen if a new delivery system for proteins were developed, heat-stable insulin were formulated, or innovative treatments for certain “orphan” diseases were found.

Figure 1.1: Combined Approach Matrix

![Combined Approach Matrix](image)

Source: Adapted from the Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options, WHO, 1996

1.8 Structure of the 2013 Report

Work on this updated report was organized in several stages. The early stages (June-December 2012) involved a review of the original methodology and collection of new, post-2004 data on disease burden and mortality. This new information is, in part, based on the 2010 Global Burden of Disease Study (GBD 2010), with its series of major publications in late 2012. These early stages led to the production of a Preliminary List of diseases and conditions for more detailed studies.

Later stages (September 2012 to May 2013) involved the production of detailed Background documents (Chapter 6), used to develop a Final List of priority diseases and conditions and their pharmaceutical gaps (Chapter 9). Any gaps that had been closed since 2004 were noted. Further updates were related to cross-cutting themes in Chapter 7: relating to the elderly, women, children and stratified medicine and enablers and barriers to innovation in Chapter 8.

Throughout the Project, an international project Advisory Group, including Member States (Belgium, the Netherlands, Portugal, Italy, UK, and Norway), members of the pharmaceutical industry, academics, nongovernmental organizations (NGOs), many patients’ groups, representatives of trade organizations, EC staff and WHO staff, met to review progress. In addition, meetings were held in Brussels with EC staff from the Directorates General (DG) for Research and Innovation and Enterprise and Industry.
Draft versions of the background documents were distributed for review and comment by external experts. An Interim Report was submitted to the EC on 28th March 2013 for review, comment and use in the priority-setting activities related to Horizon 2020 and the next IMI programme.

1.9 Issues not Addressed by the Present Study

With regard to Figure 1.1, this study focuses on BOXES 3 and 4, and not on the others. This means that the study does not address health system “access” issues where the disease condition is avertable with improved healthcare system “efficiency.” We recognize that in many cases effective medicines exist but are not fully utilized for many reasons. The issue of difficulty in physical delivery is addressed, but we have not considered the logistics or physical access in relations to effective medicines. We have also not addressed conditions which can be considered major underlying causes of morbidity or mortality, such as obesity. The study hardly mentions diagnostics or devices and does not address issues related to Intellectual Property.

Although this 2013 update will again not consider issues relating to Intellectual Property (IP), considering its continuing importance in the global debate on access to medicines and innovation, it is worth briefly reviewing the subsequent history after the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) published its report in April 2006 (REF). The CIPIH made some 60 detailed recommendations, but its central recommendation was that “WHO should develop a Global Plan of action to secure enhanced and sustainable funding for developing and making accessible products to address diseases that disproportionately affect developing countries”.

In response to the CIPIH report, the Fifty-ninth World Health Assembly agreed in 2006:

“to establish ... an intergovernmental working group ... to draw up a global strategy and plan of action in order to provide a medium-term framework based on the recommendations of the Commission; such strategy and plan of action would aim, inter alia, at securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area.” Resolution WHA59.24


The GSPA-PHI has eight elements and the seventh element on “Promoting sustainable financing mechanisms” led to the creating of another working group under the auspices of the WHO to examine current financing and coordination of research and development. It also led to proposals for new and innovative sources of financing to stimulate research and development related to Type II and Type III diseases and the specific R&D needs of developing countries in relation to Type I diseases”.

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This Expert Working Group on R&D: Coordination and Financing (EWG) was established in November 2008 and reported to the Sixty-third World Health Assembly in 2010. Some Member States indicated dissatisfaction with the EWG report so a subsequent group, Consultative Expert Working Group (CEWG) reviewed the work of the EWG and published a report in April 2012. See Updated Appendix 1.5.

1.10 Target Audience

One of the greatest challenges in regards to health is that the healthcare priorities do not always match the greatest healthcare burdens. One big challenge is that the full burden which include indirect costs such as sick leave, social benefits, early retirement and lost productivity is rarely included in prioritizations. This means that only diseases and healthcare burdens with high direct cost are prioritized. The result is that there is limited or no incentives to research within certain areas like antibiotics and psychiatric diseases. In this regard, this report aims to address different audiences. This report aims to address different audiences. The primary audience is the decision-makers working in the European Commission, Parliament, and Council who will be responsible for defining the Horizon 2020 Programme. Another crucial group are the directors of research in the pharmaceutical industry, including IMI and EFPIA. Members of the European Investment Bank, policy makers, and politicians at national and regional level may also find this report and the background documents useful for their decision making. Researchers who are deciding where to put their future efforts may find the methods and conclusions useful for their decisions. Patient groups and payers have a common interest in identifying which research may be prioritized. The level of text in the background documents is primarily geared towards technically-oriented stakeholders, whereas the level of text in the final report is primarily geared towards policy-makers.
Box 1.1: Transforming Treatment of Cancer

Gleevec®, also marketed internationally as Glivec and sometimes referred to by its chemical name imatinib, was initially approved for use by the U.S. Food and Drug Administration (FDA) in 2001 for the treatment of chronic myelogenous leukemia (CML), a rare form of cancer that affects certain types of white blood cells. Imatinib acts by specifically inhibiting a receptor tyrosine kinase enzyme that is characteristic of particular cancer cells, rather than non-specifically inhibiting and killing all rapidly dividing cells. By 2011, Gleevec® had been FDA approved to treat ten different cancers. Currently, scientists continue to study the drug’s effectiveness not only in various cancers, but also in other diseases, such as stroke (Su et al., 2008).

It has had a phenomenal success rate against CML. In one of the first clinical studies described in the medical literature, it was reported that ”[c]omplete hematologic responses were observed in 53 of 54 patients with CML treated with daily dosage of 300 mg or more and typically occurred in the first four weeks of therapy” (Druker et al., 2001). In the case of CML, patients have too many immature white blood cells in their bone marrow and blood, a complete hematologic response occurs when the patient’s white blood cell count returns to within normal range. More recently, Druker et al. found that, after 60 months of Gleevec® therapy, 98% of patients had shown a complete hematologic response. Also at 60 months, the estimated overall survival rate for patients was 89% with a relapse rate of only about 17% (Druker et al., 2006).

Arguably, Gleevec® has transformed CML treatment. In the past, the only options patients had were either bone marrow transplantation, which had serious side effects and was often fatal (and only about 20% to 25% of patients were eligible for the procedure because of age or other factors), or daily interferon infusions. The latter also had serious side effects and, moreover, was not a cure but merely a way to prolong survival. Thus, before Gleevec®, only 30% of patients with CML survived for even five years after being diagnosed (Pray 2008).

Gleevec® may be an exceptional case, and the same success may not be achieved with other cancers. Significantly, unlike most other cancers, which are caused by complex interacting factors and therefore have many potential therapeutic targets, CML is caused by a single aberrant protein related to a consistent chromosomal translocation. The Gleevec® story is a good example of how knowledge of the biological functioning of a cell can lead to life-saving medical treatment (Pray 2008).

http://www.nature.com/scitable/topicpage/gleevec-the-breakthrough-in-cancer-treatment-565


References


12 COHRED Results of the Commission’s work were published as Health Research: Essential Link to Equity in Development. New York: Oxford University Press (1990).


14 Published as Ad Hoc Committee on Health Research Relating to Future Intervention Options. Investing in Health Research and Development. WHO, Geneva, 1996 (TDR/Gen/96.1)


Appendices

Appendix 1.1  FP7 Tomorrow’s answers start today, European Commission
Appendix 1.1a  Final Conclusions and Recommendations of the Pharmaceutical Forum
Appendix 1.1b  Third meeting of the Steering Group on access to medicines in Europe, Minutes, 4 May 2011, 15.30 – 18:00, Budapest, European Commission
Appendix 1.1c  Access to Medicines in Europe Meeting on Prioritisation, Thursday, 7 April 2011 in Brussels, Minutes, European Commission
Appendix 1.2a  WHA58.27 Improving the containment of antimicrobial resistance
Appendix 1.2b  WHA60.16 – Progress in the rational use of medicines, 23 May 2007
Appendix 1.2c  WHA62.15 – Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, 22 May 2009
Appendix 1.4a  Draft global strategy and plan of action on public health, innovation and intellectual property, Priority-setting models for research and development, 20 September 2007, WHO
Appendix 1.4b  Draft global strategy and plan of action on public health, innovation and intellectual property, 31 July 2007, WHO
Appendix 1.4c  Draft global strategy and plan of action on public health, innovation and intellectual property, Progress to date in drafting groups A and B, 14 December 2007, WHO
Appendix 1.5  Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination, WHO