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 3
Approaches to Priority Setting

By Warren Kaplan, Ph.D., JD, MPH
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1 General Introduction to Priority Setting

Priority setting is a challenge at all levels (global, national, and local) and for all contexts in health systems because demand for health care usually exceeds available resources. Both consumers and funders are demanding greater accountability for how limited health resources are used to meet health system goals. Public and private sector funders must make difficult decisions about which fields and specific studies to support. Indeed, there is virtually no consensus regarding which, or whose, values should guide these decisions and how these values should inform priority setting decisions. In brief, there is no ‘best practice’. See reference 2 and Appendix 3.1. Moreover, public and private choices about allocation of resources for research needs raise social-justice issues. The ethical question is whether these funding institutions make fair decisions about where to invest their resources. Tax-payer supported institutions are clearly obliged to allocate resources in a fair manner to benefit all citizens. It is arguable that even the private sector has a responsibility to consider the public good when making research allocations.

The problem lies in deciding what qualifies as a fair allocation decision. The National Institutes of Health (NIH) lists factors that many people would use to determine fairness, but fails to rank them according to their importance. Moreover, its priority-setting criteria omit other ethical considerations that could bear on fairness, such as the relative significance of research needs of people in the United States compared to those in poor nations.

Setting priorities for health research includes two broad approaches: technical analyses which rely on quantifiable epidemiologic, clinical, financial or other data, and interpretive assessments which rely on consensus views of informed participants. Technical approaches depend on the availability of data and priorities tend to be based on these measurable units such as diseases (burden of disease) or interventions (with respect to their costs and use). See example literature on clinical trial investments or assessments of technology. The difficulty with quantitative methodology is that it hides value judgments that might reflect those of stakeholders not involved in the methodology such as users and payers of healthcare services. Indeed, as will be discussed in Chapter 4, even measuring the burden of disease itself means different things to different people. The funding priorities of the NIH demonstrates this point rather well. See section 1.2.

Interpretive or consensus stakeholder approaches relying on the subjective judgments of participants are, in theory, capable of dealing with value judgments and multifaceted assumptions, and they have been used for research priority setting in large, governmental agencies like the NIH in the USA, the Science and Technology Council of Australia, or even large pharmaceutical companies.

In various reviews and examples of priority setting exercises, it appears that an appeals process is a fundamental component to overall perceived fairness of the priority setting process. The appeals process also enhanced the involvement of stakeholders and increased overall participant satisfaction. A key lesson from this analysis is that strategic vision of the organization—both the substance and the process—will have an effect on the way that priority setting is implemented.
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This chapter reviews the various approaches which have been used to set priorities for health research in both international and national settings and explains the rationale for the choice of methods used in this project. The underlying key message is that all methods of priority-setting have limitations and different methods need to be used depending on the circumstances.

1.1 Subjective Methods for Setting Priorities

In many cases of priority setting, careful reviews the methodology assesses that the importance of research is often based on subjective judgments of reviewers and referees and the subsequent consensus that emerges from their various opinions. Such methods cannot provide a truly objective judgment, nor can there be a replicable methodology for valuing research and setting priorities since no formal measure of health research is being estimated. Such methods may be useful, however, to complement more evidence-based approaches.

1.2 Using Burden of Disease as a Benchmark

The assumption in this method is that the higher the burden, the greater the cost to society of the disease, and thus the greater the need for research. Priorities are then set based on the relative contribution of each disease to the total burden and the measure of burden ranges from epidemiologic measures to combinations of mortality and morbidity (i.e. disability adjusted life year (DALY)). See updated Chapter 4. The assumption is that the burden of disease rankings can be translated into a need for research.

1.3 Valuing Impact on Actual Clinical Practice

The impact of research on actual clinical practice has been used for prioritization based on the assumption that randomized clinical trials (RCTs) showing benefit of one treatment over another (i.e. standard treatment vs. new treatment) are likely to change current practice and thus provide a net health benefit to the population. More often than not, RCTs providing such head-to-head comparisons are not done (See original Report Chapter 8.4). Moreover, there may be more ways to modify current clinical practice than to conduct more clinical research.

1.4 Valuing Information Itself

The models for setting priorities in health recognize the uncertainty in prioritization due to the uncertainty in the factors that make up the decision. These decision-analytic methods provide some quantitative measure of that uncertainty. Different parameters are assigned probability distributions that represent how well we understand the parameters. For instance, using various computer simulations iterate the models and calculate expected costs and outcomes for treatments are calculated. Decision-analytic methods have been proposed as a framework for decision making for the UK’s National Institute of Clinical Excellence (NICE). Analysis and subjective or intuitive approaches can be identified at various places on a cognitive continuum that embodies changing ratios of analysis to intuition. Figure 3.1 is taken from the original report Appendix 3.5 and is based on the work of Kenneth Hammond at the University of Colorado, Boulder. Our methodology for prioritization uses this framework at several different places. See subsection 6.
Since 2004, there have been many attempts to describe priority setting in various contexts. Other reports have evaluated priority setting against an ethical framework. The factors that impact priority setting have been studied such as stakeholder engagement, increased dialogue, a culture supporting explicit priority setting, decision maker or group composition (size and clarity of process and local ownership, awareness, and representation), and clear information management of local politics.¹⁰

We undertook a brief literature search on PubMed to look for reviews of priority setting methods since 2004. The results can be found in updated Annex 3.1. A key conclusion of this review for the present update is that there is still very little information on how funding decisions are developed for biomedical research. We located eight reviews from 2008 to 2012.

A brief summary is listed in Table 3.1.

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**Figure 3.1. A Cognitive Continuum Framework**

![Cognitive Continuum Framework](chart.png)

**Source:** J. Dowie. In: Health Care Priority Setting. A. Oliver ed. Nuffield Trust, United Kingdom
Table 3.1 Summary Reviews of Priority Setting Methods (2008-2012)

<table>
<thead>
<tr>
<th>DATE</th>
<th>REFERENCE</th>
<th>CONCLUSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Priority Setting Methodologies in Health Research: A workshop convened by WHO's Cluster on Information, Evidence and Research (IER), its Department for Research Policy and Cooperation (RPC) and the Special Programme for Research and Training in Tropical Diseases (TDR)&quot; World Health Organization, Geneva, April 2008.</td>
<td>Legitimacy and fairness are the fundamental principles that underlie effective priority setting processes. No specific mention of prioritization for pharmaceutical funding decisions.</td>
</tr>
<tr>
<td>2008</td>
<td>Decision-making in priority setting for medicines—A review of empirical studies, <em>Health Policy</em> 86 (2008) 1–9, Vuorenkoski L, Toiviainen H, Hemminki E.</td>
<td>The clinical evidence on benefit and the quality of that evidence were the main criteria used in priority setting concerning medicines. The cost of the drug was the second major criteria in the decision-making. Two examples included priority-setting for funding medicines in outpatient and hospital settings.</td>
</tr>
<tr>
<td>2009</td>
<td>Research Priorities to Reduce Global Mortality From Newborn Infections by 2015, <em>Pediatr Infect Dis J.</em> 2009;28: S43–S48, Bahl et al.</td>
<td>Fifteen research questions received the highest scores, most were in the domain of health systems and policy research to address barriers affecting existing cost-effective interventions.</td>
</tr>
<tr>
<td>2009</td>
<td>Setting priorities for health interventions in developing countries: a review of empirical studies, <em>Tropical Medicine &amp; International Health</em> 14(8): 930–939 (2009) Youngkong et al.</td>
<td>A total of 18 studies were selected. Thirteen studies aimed primarily at identifying criteria for setting priorities in health care. Three studies explored the acceptability of using economic evaluation or burden of disease information in decision-making health priorities.</td>
</tr>
<tr>
<td>2010</td>
<td>A checklist for health research priority setting: nine common themes of good practice, <em>Health Research Policy and Systems</em> 2010, 8:36, Viergever RF, Olifson S, Ghaffar A, Terry RF, at <a href="http://www.health-policy-systems.com/content/8/1/36">http://www.health-policy-systems.com/content/8/1/36</a>.</td>
<td>Nine common themes for good practice in health research priority setting (i.e. elements of a health research priority setting process that are key and should not be overlooked) emerged and were combined into a checklist for health research priority setting</td>
</tr>
<tr>
<td>2010</td>
<td>Health research prioritization at WHO: an overview of methodology and high level analysis of WHO led health research priority setting exercises, Viergever RF, Terry R, Matsoso MP: Geneva: World Health Organization; 2010 [<a href="http://www.who.int/rpc/publications/en/">http://www.who.int/rpc/publications/en/</a>].</td>
<td>Categories of research that have been performed on research priority setting at the WHO: analysis of research priority setting practices at the WHO, normative work, provide guidance on research priority setting, and research priority setting exercises themselves that have performed research on methodologies for research priority setting as preparatory work.</td>
</tr>
</tbody>
</table>
| 2010 | Evidence-Based Priority Setting for Health Care and Research; Tools to Support Policy in Maternal, Neonatal, and Child Health in Africa, *PLoS Med* 7(7): e1000308. 10.1371/journal.pmed.1000308, Rudan I, Kapiriri L, Tomlinson M, Balliet M, Cohen B, Chopra M. | There is "currently insufficient evidence that the use of priority-setting tools improves health outcomes and reverses existing inequities. We have ample evidence that the lack of a rational and transparent process generates inequity and stagnation in mortality levels."

2012 | From efficacy to equity: Literature review of decision criteria for resource allocation and healthcare decisionmaking, *Cost Effectiveness and Resource Allocation* 2012, 10:9 doi:10.1186/1478-7547-10-9, Guindo et al. | The most frequently mentioned criteria were: equity/fairness (32 times), efficacy/effectiveness (29), stakeholder interests and pressures (28), cost-effectiveness (23), strength of evidence (20), safety (19), mission and mandate of health system (19), organizational requirements and capacity (17), patient-reported outcomes (17) and need (16). |
2 Definition of “Priority” Medicines

2.1 Drug Regulatory Authority Priority Setting and Innovation

We briefly review how the drug regulatory agencies of the United States (USA), the European Union (EU), and Canada define a “priority” medicine.

UNITED STATES

The classification system of the United States Food and Drug Administration (FDA) assigns all new drug approvals to categories representing distinct levels of innovation and this classification is relevant for our purposes as it highlights the different meanings of the term “innovation”. The FDA reviews new drug applications (NDAs) and awards priority status based on its chemical type and therapeutic potential. With regard to the latter, a drug qualifies for priority review because it is a significant improvement over marketed products. With regard to the former, a new molecular entity (NME) is a drug whose active ingredient has never before been approved by the FDA for the United States market. An incrementally modified drug (IMD) is one that relies on an active ingredient present in a drug already approved for the United States market or a closely related chemical derivative of such an ingredient that has been modified by the manufacturer. “Other” drugs are drugs with an active ingredient that is already available in an identical marketed product. A “standard drug” is a product that does not qualify for priority review and can also be an NME, IMD, or “other”. Most observers in the United States would view priority NMEs as the most innovative type of new drug.

The FDA has also granted priority status to some IMDs indicating that they provide therapeutic advances even though they are derivatives. Priority IMDs are also moderately innovative. The FDA, however, rates many NMEs as standard and, although based on new compounds, these drugs usually have the same mechanism of action and outcomes as other drugs on the market. Standard NMEs may have different safety and efficacy profiles from other marketed drugs in the same class. Thus, standard NMEs may enhance clinical outcomes even if they do not demonstrate significant improvement over other medicines already available.12

We further note that the Institute of Medicine (IOM) Report on the National Institutes of Health (1998) 13 investigated the research prioritization in the NIH. Research prioritization within the NIH varies by institute. The National Eye Institute has a formal planning process, although details are not known at this time. The National Cancer Institute (NCI) plans, promotes, and carries out disease-specific research through advice from expert Progress Review Groups (PRGs) using an interpretive/consensus stakeholder approach.

Components of Prioritization in the FDA:
Fast track is a process designed to facilitate the development and expedite the marketing review of drugs to treat serious diseases and fill an “unmet medical need”. Determining whether a disease is serious is generally based on whether the drug will have an impact on factors such as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Filling an “unmet medical need” is defined as providing a therapy where none exists or providing a therapy
that may be potentially superior to the existing therapy. If there are existing therapies, a fast
track drug must show some advantage over the available treatment, by showing superior
effectiveness, avoiding serious side effects of an available treatment, improving the diagnosis
of a serious disease where early diagnosis results in an improved outcome, or decreasing a
clinically significant toxicity of an accepted treatment.

Most products that are eligible for fast track designation are likely to be considered
appropriate to receive a priority review. The FDA goal for reviewing market authorization
for a drug with priority review status is six months. A drug that receives fast track and also
Priority Review) designation is eligible effect for more frequent contact with the FDA. The
drug is also eligibility for a third component of prioritization: accelerated approval where
marketing approval of an effect on a surrogate, or substitute endpoint is likely to predict
clinical benefit. All of these procedural measures indicate a willingness of the FDA to
prioritize applications to accelerate regulatory review prior to market authorization. The
FDA criteria are similar to those used in this report.

**Priority Review Vouchers:**

Priority review vouchers area prize incentive for companies to invest in new drugs and
vaccines for neglected tropical diseases. A provision of the FDA Amendments Act (HR 3580)
awards a transferable “priority review voucher” to any company that obtains approval for a
treatment for a neglected tropical disease. The voucher, which is transferable and can be
sold, entitles the bearer to a priority review for another product.

It has been estimated that priority review can cut the FDA review process from an average of
18 months down to six months, shortening by as much as a full year in the time it takes for
the company’s drug to reach the market.14

For a company with a top selling drug with a net present value close to US$ 3 billion, it has
been estimated that the accelerated approval could be worth over $300 million.14 At this level,
the voucher would be expected to offset the substantial investment and risk required for
discovery and development of a new treatment for a neglected disease. If the time saved
from gaining a priority review is much shorter, then the value of the voucher will be
significantly less.

Companies that use the voucher will be required to pay a supplemental priority review user
fee to ensure that the FDA can recuperate the costs incurred by the agency for the faster
review. The additional user fee also aims to ensure that the new program will not slow the
progress of other products awaiting FDA review.

**EUROPEAN UNION**

European Union (EU) products are eligible for priority review by the European Medicines
Agency for the Evaluation of Medicinal Products (EMA) if they claim to provide a significant
improvement compared to marketed products in the treatment, diagnosis, or prevention of a
disease. This is not the same as “fast track” status in which the license processing time is
approximately halved. The EU system grants this accelerated approval based on the
seriousness of the disease, the absence or insufficiency of an appropriate alternative, and the
anticipation of high therapeutic benefit.15
Soon after the original *Priority Medicines Report* was published, so-called “accelerated assessment” was introduced by revising the EU pharmaceutical legislation in November 2005. Companies can request accelerated assessment provided they are able to demonstrate that their product responds to unmet medical needs or constitutes a significant improvement over the available methods of prevention, diagnosis, or treatment of a condition.

An accelerated assessment is conducted in a maximum of 150 days. The normal timetable for the centralized procedure allows a maximum assessment period of 210 days. In 2006, 13 requests for accelerated assessment were received, four of which were accepted. The first product to be accepted was Soliris® (eculizumab), from Alexion Europe SAS, which is a designated orphan medicinal product. This drug is intended to reduce haemolysis (destruction of red blood cells) in patients with paroxysmal nocturnal haemoglobinuria (PNH), a rare blood disorder in which the red blood cells are weak and are thus destroyed more rapidly than normal causing the urine to turn red or dark during an episode (or paroxysm) of haemolysis. See updated Appendix 3.2.1a. See Guidelines in the updated Appendix 3.2.1b

**CANADA**

Priority medicines in Canada are those for a serious, life-threatening or severely debilitating illness, or condition for which there is substantial evidence of clinical effectiveness. Specifically, the drug must provide effective treatment, prevention, or diagnosis of a disease or condition for which no drug is presently marketed in Canada. Alternatively, the drug must provide a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is improved over existing therapies. The risk-benefit evaluation in Canada may include:

- Improvement in one or more of the serious outcomes.
- A favourable effect on a serious symptom of the condition for which there is no existing therapy.
- A clinical benefit in individuals unable to tolerate, or unresponsive to, existing therapies.
- Demonstration of effectiveness in combination with other critical agents where no information is available.
- Demonstration that the new agent is able to provide clinical benefits that are similar to existing therapies while a) avoiding serious toxicity present in existing therapies and/or b) avoiding less serious toxicity, common to the therapy, which results in the discontinuation of treatment for a serious disease. See Canadian Ministry for Health.  

A revised policy statement on priority medicines in Canada became effective as of 1 March 2006 and replaced the previous policy dated 1 November 2002, but there were no substantive changes. Guidance document in updated Appendix 3.2c.
3 Public Sector Priority Setting: National Institutes of Health, Global Forum and Others

Over the past decade, attempts at priority setting for health sector research have been made by public sector organizations such as the NIH, the Global Forum for Health Research, Special Program for Research and Training in Tropical Diseases (TDR), and other WHO collaborations. We provide brief summaries of a few of such approaches.

**National Institutes of Health (NIH)** (1998 officials issued a document explaining their allocation criteria in 1997. See Appendix 3.3a. Five considerations play a role in decisions about funding biomedical research: (1) public health needs, (2) scientific merit of specific study proposals, (3) potential for advances in a particular area, (4) distribution across diverse research areas (because it is impossible to predict exactly where advances will occur), and (5) national training and infrastructure needs.

The first NIH criterion for public health needs is determined by the number of people with a specific disease, number of deaths a specific disease causes, degree of disability a specific disease produces, how much a specific disease shortens the average human lifespan, a specific disease’s financial and social costs, and threats posed to others by contagious disease. According to the NIH, these considerations are of equal importance in allocating research resources. See Appendix 3.3a (National Institutes of Health. *Setting Research Priorities at the National Institutes of Health*. Bethesda, MD: National Institutes of Health. 1997).

We note that, as of 2004, only four institutes of the NIH, the National Cancer Institute (NCI), National Institute of Child Health & Human Development (NICHD), National Institute on Aging (NIA) and National Institute of Environmental Health Studies (NIEHS) had capability of retrieving bibliometric data to track the publications and assess the potential public health impact of their grantees. Three institutes (NIEHS, NICHD and NIA) collaborated to develop a database to improve the priority-setting process. The Office of Portfolio Analysis (OPA) was only recently established in 2011 by the NIH to “enable NIH research administrators and decision makers to evaluate and prioritize current, as well as emerging areas of research that will advance knowledge and improve human health.” (NIH, OPA at http://dpcpsi.nih.gov/opa/index.aspx, last accessed 20 September 2012).

At present, the NIH lacks a comprehensive ability to track awards, output, and subsequent health impact of awards. For instance, with regard to patents and licensing of intellectual property, no database exists for NIH-funded patents and university licensing. Furthermore, with regard to the practical output of awarding NIH grants, there is inadequate linkage between NIH awards and the resulting literature or citation data. In this regard, a preliminary bibliometric analysis suggests that the impact of an R01 grant is predicted more accurately by a publications impact factor than the number of subsequent citations of the investigators. At a recent Portfolio Analysis Workshop (July 23-24 2012) a survey of over 500 participants showed that 47% of the participants thought that measuring the impact of NIH grants would be the most important job of the OPA.

Since the late 1980s, there have been many attempts by various international organizations and less formal groups to develop methods for prioritizing health research (see also 2004 Report Chapter 3 Annex 3.1). During the 1990s, a series of commissions undertook studies...
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aimed at priority setting for health or for health research, but none of these specifically focused on pharmaceutical research. The studies are summarized below in roughly chronological order:

The Commission on Health Research for Development (COHRD) (1990) was an independent international initiative formed in 1987 with the aim of improving the health of people in developing countries through a focus on research. The idea of country-specific research became manifest as the Essential National Health Research (ENHR) concept. See original Appendix 3.1.

The 1993 World Development Report (WDR) was the 16th in a series of World Bank reports and was prepared in conjunction with the WHO. Probably the greatest value-added was the use of the DALY – arguably a major advance in methodology to help guide resource allocations towards reducing the greatest burden of disease for which there are cost-effective responses. See original Appendix 3.2.

The Ad Hoc Committee on Health Research (1996) was established under the WHO auspices and was formed based on the previous conclusions of the WDR, as well as the interests of funders and foundations in health research and development (R&D). The Committee focused on needs of low to middle-income countries, but realized that private sector product development considerations (i.e. magnitude of the problem and basing cost-effectiveness of new therapies and products on scientific judgment) can also create discussion about priorities for a public sector R&D. A major contribution of this document was the identification of specific high-priority product development opportunities using a systematic “5 step” process.

The WHO Advisory Committee on Health Research is the primary WHO expert advisory body on scientific research and practices, and their role is to analyze health status to guide a global health research agenda. Their methodology for setting research criteria is written in broad terms. See updated Appendix 3.3b.

The Global Forum for Health Research has created a framework, Combined Approach Matrix, which brings together in a systematic manner all information related to a particular disease or risk factor. This framework is a very useful way of organizing information. It identifies gaps in knowledge and future challenges. In part, its value is in its ability to help set priorities for national, regional, or global diseases. See original Appendix 3.6.

The framework allows identification of common factors by looking across diseases or risk factors. Completing the matrix should highlight the blank areas (i.e. where there are gaps in information needed to make rational decisions). We have based our approach, in part, on this methodology. See Section 3.

The UNICEF-UNDP-WB-WHO Special Programme for Research and Training in Tropical Diseases (TDR) prioritizes on a disease-by-disease basis. TDR has previously completed a prioritization exercise for African trypanosomiasis, dengue, leishmaniasis, malaria, schistosomiasis, tuberculosis, chagas disease, leprosy, lymphatic filariasis, and onchocerciasis. For each disease, the analysis was undertaken by the TDR in consultation with outside experts. See original Appendix 3.4.
In 2008, TDR convened over 130 experts to work in ten disease-specific and thematic reference groups to carry out a review and consultation process and identify top research priorities. Each reference group was jointly led by a disease endemic country and international chair or co-chair, and each was hosted by a disease endemic country with the WHO country or regional offices acting as the secretariat. The analysis and research priorities developed by these expert groups was followed by regional and national consultations with stakeholders and workshops. Developed over three years and in three phases, The Global Report for Research on Infectious Diseases of Poverty identifies research-related actions that policy-makers, funders, and researchers should focus on if the public health challenges of infectious diseases of poverty are to be met. The report details the drivers of infectious diseases in poor populations and highlights how advances in science and technology can be used to meet the challenges of controlling these diseases. The report was produced in 2012. See updated Appendix 3.3c.

WHO-IFPMA ROUND TABLE: In 2000-2001, a joint task force comprising members of the WHO and the pharmaceutical industry convened to establish a working list of infectious diseases and review disease burden as a way of directing research priorities. In addition to DALYs, the criteria used for assessing disease impact included mortality, societal costs, likelihood of treatment, and forward trends. Members of the roundtable then reviewed existing interventions on the basis of availability and limitations of medicines. Current levels of industry activity for each disease were assessed. A judgment on the need for additional medicines R&D was, therefore, made on the basis of the current or likely future availability of medicines and other treatment approaches. Altogether, combinations of 17 assessment criteria were used. See original Appendix 3.7.

WHO Priority Setting Methodologies in Health Research (10-11 April 2008): A workshop on Priority Setting Methodologies in Health Research was held at the WHO in Geneva, Switzerland from 10-11 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, reviewed the main priority setting methodologies utilized to date, reviewed and assessed case studies of priority setting in various countries and for various topic areas, and developed a framework of guiding principles and a practical approach to priority setting by bringing together salient elements of existing methodologies See updated Appendix 3.3d.

Review of Health Research Prioritization at the WHO (ENHR) (2010): In 2010, the Department of Public Health, Innovation and Intellectual Property of the WHO along with the Department of Research Policy and Cooperation wrote a review (see updated Appendix 3.1) in support of element 1.1 of the Global Strategy and Plan of Action on Public Health, Innovation, and Intellectual Property (GSPOA) on public health, innovation, and intellectual property and the Priorities Goal actions (a) - (d) of the WHO strategy on research for health.

The GSPOA was adopted by the 61st World Health Assembly (WHA) in 2008. [World Health Assembly resolution 61.21 Global strategy and plan of action on public health, innovation, and intellectual property, 2008.] See also updated Appendix 3.3e Element 1.1 (a) of the GSPOA reads that action needs to be taken to:
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“1.1 (a) Develop methodologies and mechanisms to identify gaps in research on type II and III diseases and on developing countries’ specific R&D needs in relation to type I diseases”.

The review found that there is a wide variety of research priority exercises undertaken at the WHO. A review of the methods indicates there is no gold standard or best practice in setting research priorities, but a list of 10 themes of good practice when undertaking a research priority setting exercise was developed. Most of the methods reviewed involved stakeholder meetings to identify consensus, but the use of an “established priority setting tool was rare.” We reproduce this checklist in its entirety. See also updated Appendix 3.1.

This approach was developed to define: who sets priorities and how to get participants involved; the potential functions, roles and responsibilities of various stakeholders; information and criteria for setting priorities; strategies for implementation; and indicators for evaluation. It was designed to not only specify broad research areas but also give a detailed listing of priority possibilities/options as well as to involve a broad range of stakeholders and significant engagement with experts. Significantly, discussion and decisions on funding are supposed to be based on tapping the skills and knowledge of scientists from a wide range of disciplines.

The Child Health and Nutrition Research Initiative (CHNRI)
This approach emphasized principles of legitimacy and fairness and provided a detailed listing of individual research questions scored against pre-defined criteria. Technical experts independently scored each research option against these five criteria. As in other methods, stakeholder input was sought and used to rank the five criteria from the most important to the least important. These rankings were then adjusted to provide relative “weights” that determined the importance of the research option. Everything is recorded, is repeatable, can be reviewed, and can be challenged and revised at any time based on feedback, so this is a very dynamic process. The role of non-experts was limited to selecting and weighing criteria. Once consensus is reached on areas of research there is no further stakeholder involvement.
Table 3.2: Checklist for health research priority setting

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<tbody>
<tr>
<td><strong>1. Inclusiveness</strong></td>
<td>Who should be involved in setting the research priorities? And why?</td>
</tr>
<tr>
<td><strong>2. Preparatory work</strong></td>
<td>Can include literature review, collection of technical data or broader stakeholder views</td>
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<tr>
<td><strong>3. Global - National</strong></td>
<td>Exercises from different levels can be used to inform each other in both directions</td>
</tr>
<tr>
<td><strong>4. Context &amp; Values</strong></td>
<td>Context and values underpin the process</td>
</tr>
<tr>
<td><strong>5. Implementation</strong></td>
<td>Think about options for translation to policy and funding from the beginning of the process</td>
</tr>
<tr>
<td><strong>6. Criteria</strong></td>
<td>Criteria help focus discussion around research priorities on key dimensions of research options</td>
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<tr>
<td><strong>7. Ranking process</strong></td>
<td>One can opt for a ranking or consensus based approach, or both</td>
</tr>
<tr>
<td><strong>8. Use of a tool</strong></td>
<td>The value of using a tool lies in the minimization of the possibility of forgetting important aspects of research priority setting</td>
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<tr>
<td><strong>9. Re-evaluation</strong></td>
<td>Research priority setting is not a solitary exercise</td>
</tr>
<tr>
<td><strong>10. Transparency</strong></td>
<td>Report on: Who set the priorities? How exactly were the priorities set?</td>
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The Consultative Expert Working Group (CEWG) and Priority Setting (2012)


A second consultation was initiated by the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) and the 20 members of the CEWG group, representing all WHO regions, published in April 2012 an analysis titled "Current financing and coordination of research and development, proposals for new and innovative sources of financing to stimulate research and development related to Type II and Type III..."
diseases, and the specific research and development needs of developing countries in relation to Type I diseases”. See updated Appendix 3.3g. This report further analyzed a series of proposals to accomplish this de-linking. Both reports have engendered much subsequent and ongoing work in this area, but are not the subject of this updated Background document, which is restricted to prioritization in the biomedical R&D process. However, the CEWG recommended the promotion of partnerships and collaborations based on joint agendas and priority setting related to the health need and national plans for essential health research in developing countries.

We note with interest one particular proposal for a Global Framework on an R&D Treaty sponsored in part by Health Action International (HAI) Global. Their submission stresses the “paramount importance of exploring and supporting an international instrument to address the coordination, financing, and norm setting for biomedical R&D.” According to HAI, these aspects are “the only way to achieve a realistic structural change in R&D priority-setting focused on needs-driven research.” See CEWG submission. Comments by HAI Global. Submitted by Health Action International (HAI) Global, HAI Latin America and the Caribbean (AISLAC) and HAI Europe (HAI-E), 2011.29

In June 2012 the European Commission (EC) met to debate on the recommendations from the Consultative Expert Working Group on R&D (CEWG) report (see updated Appendix 3.3h). Most of the recommendations were specific to creating new ways of sustainably financing biomedical R&D that are informed by this “de-linking” method mentioned above. Nonetheless, with respect to prioritization of R&D, the EC noted the following: higher priority needs to be given to R&D on neglected diseases within Horizon 2020 and the EDCTPA compromise should and can be found between EU market interests and developing country needs (e.g. through promoting private-public partnerships). A “truly open innovation model based on more systematic and efficient information sharing by all stakeholders, including the pharmaceutical industry” was deemed critically important. Finally, improving priority-setting was critical, particularly the alignment with the public health needs of developing countries, decision-making relying on transparent governance structures, and giving developing countries a strong voice.

### 4 Private Sector: Prioritizing Pharmaceutical R&D Private Sector “Unmet Needs” Assessment

Pharmaceutical, biotechnology, and other companies are profit-making entities that consider the size of anticipated financial return as an essential guide to research investments. Although pharmaceutical companies tend to have relatively high profit margins they also take substantial financial risks when they develop new drugs.

Pharmaceutical and biotechnology companies set R&D priorities based on market potential, liability costs, the scope of intellectual property protection, market lead time, the expected time from the laboratory to the market, and other factors that affect the profitability of a research investment (see Section 4.1). As a result, they tend to shy away from investing their funds on basic research, rare diseases, diseases with low consumer demand, drugs that will take a long time to get to the market, or drugs that have high liability costs. However, the
industry’s investment in some of these areas is slowly gaining ground when adequate incentives are created. See original Background document Chapter 8.1 and associated Annexes.

4.1 Pharmaceutical Company’s Product Development Strategy

Based on discussion with industry executives, the general process employed by the pharmaceutical industry is that there is no “generic” method for determining unmet medical need or for creating a product development profile since each organization has different needs and agendas. However, most companies combine commercial market research, competitive intelligence, and therapeutic strategies with scientific development to determine their therapeutic product profile. Decisions about new drugs are generally made within a set of four different contexts: scientific opportunity, market assessment, available human and organizational resources, and medical need. From a marketing viewpoint, a classic market-based series of steps might occur as follows:

- Review the marketplace to identify unmet medical needs. This involves reviewing the therapeutic area to understand the state of practice and to identify key market openings that reflect this unmet medical need. This task requires interpreting complex epidemiological and economic data where there are not accepted definitions of need. How does one balance the need for new treatments for rare and fatal conditions with the need for palliatives for common diseases that produce disability, but not death? See Subsection 4.2.

Factors to guide in the consideration of treatments:
- Benchmark competitor products to understand the competitive landscape.
- Identify the market segments and patient populations a product will target.
- Identify all possible indications that might make the compound more valuable. Often, companies seek to introduce more indications and line extensions earlier in a product lifecycle to maximize a molecule’s lifetime economic value.
- Create a dosing and delivery profile to provide optimal dosing and delivery mechanisms.
- Understand the broad market preferences for the key characteristics of the product so that commercial perspectives are embedded early on in the product development cycle. The goal of market research at this point would be to find a product profile that physicians would prescribe at levels needed to justify further development.
- Assemble market research to profile key geographic markets to ensure product marketing success.
- Create an ideal new product launch profile since marketers note the importance of identifying characteristics that would enable a fast uptake launch for the new product.

There are numerous tools and tactics to make these assessments. These include structured processes to guide teams through critical discussions, milestones, sophisticated decision trees, and complex econometric forecasting to integrate several decision factors with use of historical benchmarks of past project from similar areas. We note that overly complex and financially driven models can provide a false sense of certainty into an inherently risky endeavour.
4.2 Determining Unmet Medical Need: Company A

One of the largest innovative pharmaceutical companies shared their approach to determining unmet medical needs with collaborators of this report. They have found that determining and measuring unmet needs is not straightforward. Many factors contribute to an individual’s perception of unmet needs and these will vary between people and on different diseases. Recognizing this, company A established a systematic method in the 1990s to measure perceptions of unmet needs among its customers. The process started with qualitative market research among doctors in the United States and Europe to determine what they believed were key components of unmet medical needs. These components varied from the extent of physical or psychological suffering the disease imposed on the patient, the financial impact of the disease, the likelihood of complications, and to the effect they have on careers. In total, 18 major classes of factors were identified. The company discovered that healthcare providers in the United States and Europe viewed unmet medical needs in a similar fashion. Hence, the company developed their unmet-needs model with doctors in the United States while having the model also be appropriate in the European setting.

Following the initial qualitative phase, the company embarked on a major piece of quantitative market research whereby over 700 primary care doctors and specialists in the United States ranked over 600 conditions against these 18 factors. The end result of this process is that an unmet need score can now be associated with any disease from the prescriber’s perspective. Based on unmet needs, the company can determine which diseases are more significant as perceived by primary care and specialist prescribers.

By further studying the data, the company has been able to determine the drivers of the unmet need for each disease so they were able to direct their research efforts. Finally, using a decision tree approach, the company was able to determine the extent to which the unmet need might be reduced if a new therapy were introduced. The company has repeated this market research routinely because it is recognized that unmet need is not static. As new treatments are introduced, perceptions of unmet needs change and need to be continually monitored.

4.3 Determining R&D Funding Sources for “Neglected Disease”: G-FINDER

Donors interested in funding R&D of neglected disease products must currently make substantial investment decisions in the absence of accurate data regarding funding flows, gaps, and duplications. Information that is available is often out of date, incomplete, unreliable, or cannot be compared across surveys due to different accounting and reporting methodologies. In some areas there is an almost total lack of information.

The goal of the G-FINDER survey is to help funders better target their investments into neglected disease product R&D. See http://g-finder.policycures.org/gfinder_report. G-Finder tracks global investment annually in this area. By providing funders with better information, the goal of the G-FINDER survey will help stimulate increased efficiency and investment into neglected disease product R&D. The G-FINDER survey includes 31 neglected diseases, and the pharmaceutical tools used to prevent, control, and treat these diseases. The pharmaceutical tools include drugs, preventive and therapeutic vaccines, diagnostics,
microbicides, and vector control products. The survey encompasses R&D funding for these products from basic research through clinical trials.

Their most recent report (Appendix 3.4) reflects the global economic challenges which are still with us. The total reported funding for R&D of neglected diseases in 2010 was US$ 3 063 million (US$ 3 173 million unadjusted 2010). This was a decrease from 2009. The effect of the global financial crisis became evident with large funding cuts across all sectors except the pharmaceutical industry. The three ‘top tier’ diseases received most of the global funding for neglected disease R&D; HIV/AIDS (US$ 1 073 million, 35.0%), tuberculosis (TB) (US$ 575.4 million, 18.8%) and malaria (US$ 547.0 million, 17.9%) –. However, their share of global funding continued to fall. Thirteen of the top 20 governments cut their neglected disease R&D funding in 2010, as did eight of the top 12 government funders who represent 93.1% of total public funding. The United States is still by far the world’s largest government funder contributing nearly 70% of global public funding (US$ 1.39 billion, 69.7%). However, its funding dropped in 2010 (down US$ 74.5 million, -5.1%), driven by a US$ 44.5 million drop in NIH funding. The United Kingdom was one of the very few countries where public funding for neglected disease R&D increased (up US$ 21.2 million, 14.9%). The majority of other governments cut their funding in 2010, including the European Commission (EC) (down US$ 25.8 million, -21.8%). Philanthropic funding also decreased by a US$ 79.8 million (-12.4%) in 2010.

5 Prioritization in Other Contexts

5.1 Public Private Partnerships: Innovative Medicines Initiative

The IMI Scientific Research Agenda (SRA) is a multiannual research plan to set research priorities of IMI. The priorities defined in the Research Agenda are the basis for the research topics of the annual calls for proposals. Scientific advances and changes in the industry led the IMI Scientific Committee to initiate the revision of the original 2008 SRA in 2010. For the 2008 SRA, see updated Appendix 3.5a.

In 2010, the Scientific Committee produced a Status Report, “Trends, Challenges and Opportunities in Drug Research” which provided an overview of what they see as innovative research opportunities existing in the academic or small medium enterprises (SME) world. Following the Status Report, the IMI Executive Office, and the Scientific Committee organized a series of workshops to solicit ideas and feedback from stakeholders including industry, academia, regulatory authorities, and patient organizations. During the summer of 2010, feedback and comments on the Scientific Committee’s Status Report were provided by the European Federation of Pharmaceutical Industry Associations (EFPIA) Research Directors Group (EFPIA) and proposals for the future strategic research themes were given. The process included consultation of stakeholders and resulted in a revised SRA in 2011. See updated Appendix 3.5b.

According to the IMI documents (updated Appendix 3.5c), the evaluation and selection processes for IMI priorities are based on the following key principles: scientific excellence, transparency, fairness and impartiality, confidentiality, efficiency, speed, and attention to ethical considerations. Notwithstanding the extensive consultations, none of the documents listed above describes the methods used to arrive at the research priorities for the IMI.
5.2 Examples of Priority Setting at a Local Level

Albeit on a different scale than the EU, the issues raised in priority setting at more local levels are illustrative and we briefly discuss two of these below.

a. Hospital Formulary Committees

Priority setting for new drugs in a hospital context, such as in a hospital drug formulary committee, is based on a complex array of factors that include clinical evidence, adverse reactions, availability of alternate drugs, ease of administration, cost of the drug as compared to current drug cost, and comparative advantages between drugs. Formulary committees do not review all these factors, but rely on clusters relevant to each decision. In this case, decision making is highly dependent on context.

Studies have described decisions regarding new drugs as being based on: “thresholds” determined from information on effectiveness, generic substitution principles, or other, somewhat, limited survey information or decision making techniques.

b. The Oregon Experiment

In the late 1980s Oregon, a state in the north western part of the United States, decided to expand Medicaid coverage from low-income individuals to a greater number of people. Oregon formulated an explicit process for setting priorities in health services. The members involved in the Oregon methodology were five primary care physicians, a public health nurse, a social worker, and four members of the public. They drafted a list of services ranked according to priority of importance based on considerations of clinical effectiveness and social values. Panels of physicians rated the clinical effectiveness of approximately 1000 condition-treatment pairs. Public input was sought to integrate social values into the priority list. There was widespread criticism of some of the rankings; this was related in part to the poor data on effectiveness and on how people view health utilities. A brief review of this list is in updated Annex3.1.

c. Involving the public in research funding allocation: A pilot project

Since the original Priority Medicines Report, the idea of involving the public in research funding decisions or research priority setting has emerged as a significant topic. Various groups have analyzed strategies for patient participation in biomedical research priorities and concluded that there is little evidence for strategy effectiveness.

Recently, a small pilot study asked members of the public to select which of four potential projects (about food-related topics presented by scientists) ought to be funded. The study was methodologically weak and the relatively small number of participants were not particularly representative of the general public such that they were better educated than the

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* Public preferences for a variety of health states were obtained by a random telephone survey. Meetings were held across the state to assess the public's values regarding various health services. Public meetings were held to allow input from special interest groups regarding specific services.

* Hypothetical choices about severe medical conditions elicit different responses when the choices are placed in a social context as people tend to give such conditions much more weight (See endnote 18).
norm. Results suggested that participants’ funding decisions were largely based on factors such as “benefit to society” and “personal relevance” – factors clearly related to public health approaches to prioritization. The following quote highlights the contextual issues as such:

“Indeed, how should the public be involved? Should it be used to sift the relevant from the irrelevant? Should it have authority to give final approval to a number of short-listed proposals that have already passed some assessed threshold of scientific merit? Or should the public simply be available to passively absorb facts and give an appearance of involvement that is not in fact genuine? It is likely that different organizations possess different takes upon this issue, and that lack of clarity and confusion of purpose is a boon to some who are not convinced in the merits of the public involvement argument.”

A larger study was recently conducted (see updated Appendix 3.5.1c) which analyzed a very focused research prioritization advisory project initiated by the Dutch government in 2010 in which a wide diversity of patient groups were actively involved. This study brought forth two main issues: 1) how to find a balance between a predefined focus and being sufficiently broad to enable patients and patient representatives to contribute and 2) how to find a balance between relevance for many patients groups and too much data for a lower number of patient groups. See also Appendix 3.5.1c and in press as: Elberse JE, et al. Patient involvement in a scientific advisory process: Setting the research agenda for medical products. Health Policy (2012), http://dx.doi.org/10.1016/j.healthpol.2012.05.014

All these questions are clearly relevant and much more work needs to be done on determining when and to what extent the public should be involved in research funding decisions. This report update intends to delve more deeply into these and other questions in this regard.

6 Prioritizing for the Priority Medicines Project

6.1 Background: Solving Problems and Making Decisions

If we agree that resources for pharmaceutical R&D are substantially limited, but the needs and demands for health interventions are sufficient, then R&D resource allocations are based on rationing decisions. Due to cost and other constraints, rationing in this situation implies that not every disease condition will get every medicine that is needed, wanted, or even deserved. Prioritizing, fixing agendas, setting goals, and designing actions are usually called “problem solving” and evaluating and choosing among alternative actions is called “decision making”.

Many problems (i.e. designing a building or creating a public health based pharmaceutical R&D prioritization) have complex, ambiguous goals and are constantly shifting or transforming in the course of exploring the problem. Much of the research about organizational decision-making in management studies, industrial sociology, and organizational psychology reveals that organizational decision-making is often messy, implicit, intuitive, and ill-defined.37
Update on 2004 Background Paper, BP 3 Approaches to Priority Setting

The goals of a public health care system are a complex amalgamation of a number of other goals, not all of which are readily defined. Thus, the use of any one tool to set priorities within such a complex entity may be overly simplistic. Indeed, evidence shows that allocations of research funds by the NIH, largely through informal and unstructured processes, turn out to be consistent with measurements of disease burden (a criteria used in more formal priority setting models).

This complexity is further underscored by Holmstrom (1999), who stated that:

“Priority-setting is a complex interaction of various decisions at diverse levels in the organization. There is no self obvious set of ethical principles or scientific tools to determine what decisions we should take at various levels, nor is there an easy or obvious way to determine what decisions we should take at various levels, nor is there an easy or obvious way to resolve the dilemma of the increasing gap between what we can and would like to do on one hand and the resources on the other.”

There is no one correct answer, and there may not even be an answer. At the very least, there will be moral disagreements over any decisions that are made. For example, setting pharmaceutical research priorities based on principles of efficiency may lead to very cost-effective interventions that cannot be offered to everyone because of the expense, thereby, violating the principles of equity.

6.2 Priority Setting as a Political Process

The question then becomes whether priority setting is, or can be, a truly rational undertaking or whether it is essentially a value-based political process. Priority setting in health care at the level of the European Union involves inadequate information, uncertainty, and conflicting interests among many people with varying goals and values. Ultimately, it is a political process, which involves “pluralistic bargaining between different lobbies, modified by shifting political judgements made in the light of changing pressures.” Under such circumstances, what is required may be an explicit framework that allows stakeholders to debate about what values should be used to set priorities. This suggests that a truly comprehensive process of priority setting requires public input (to understand individual and societal principles) and accountability (to make explicit the rationale for decisions).

6.3 Putting Explicit Models in Perspective: Providing a “Menu” for Policy Makers

We believe there is no best way to prioritise pharmaceutical R&D in a public health context. Such prioritization should be viewed not as a problem to be solved, but as a multidimensional dilemma.

There are principles of allocation that can be thought of as a series of non-exclusive items on the continuum shown in Figure 3.1 as a “menu” that policy makers might consider. We briefly discuss these allocation principles and then summarize how policy makers might use them to prioritize pharmaceutical R&D.

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*Dilemma: “Any situation necessitating a choice between unpleasant alternatives”, Webster’s New World Dictionary, 1960, World Publishing Company, USA*
a. The "Evidence Based" Approach: Modes 1 and 2 in Figure 3.1
(For example, acute stroke, chronic obstructive pulmonary disease (COPD), Alzheimer disease)

We have combined burden of disease analysis and an assessment of clinical efficacy of interventions for diseases using rankings for burden of disease and the Cochrane Reviews of randomized clinical trials. See updated Chapter 4 for further details of the burden of disease method and the clinical trial reviews. Each of the burdens of disease and clinical efficacy analyses has important limitations which are further discussed in Chapter 4. At best, the combination of burden of disease and clinical efficacy provides a preliminary and retrospective review. Furthermore, the Cochrane Reviews analysis allows us to see if, overall, certain medicines show a clinical efficacy, which is unequivocally better than placebo. Both ever and very old therapeutic interventions will not be found in the Cochrane Reviews (see updated Chapter 4). While we have analyzed the risk of side effects, we have not been able to incorporate this data into our priority setting as the quality of the data was not consistent. See original Report Chapter 5 and the original Report Annexes to Chapter 5.

b. Priorities Based on Predictions and Probabilities: Modes 5, 6, and 7 in Figure 3.1.
(For example, antimicrobial resistance (AMR), pandemic influenza)

What are the emerging diseases that will affect the European Union and the world going forward? What existing diseases or risk factors will grow in importance? The answers to these questions form our second prioritization method and are based primarily on consensus judgments and observational and clinical evidence. Antibacterial resistance is not a disease condition per se, but we believe its importance as a threat to global public health will continue to grow. Few, if any, clinical trial reviews on HIV or diabetes have yet found their way into the Cochrane database. As a result, we have relied on the predictive power of other evidence and the views of experts in the field to develop priorities.

c. Priorities Based on Social Justice: Modes 5, 6 and 7 in Figure 3.1
(For example, rare or neglected diseases)

There are many perspectives one can take with regard to pharmaceutical research priority setting in terms of the Priority Medicines Project. One can conceptualize priority setting within a legal context as emphasizing universal rights to health care, a medical perspective as relying on evidence-based medicine, or an economics perspective as emphasising cost-effectiveness analysis. Recently, many have argued that priority setting is an ethical exercise that requires moral reasoning.41 We have chosen to emphasize the ethical and moral aspects of priority setting as our third prioritization method along the continuum shown in Figure 3.1. Many European countries have a long history of social solidarity, which has been demonstrated by the creation of universal social security systems and national health systems to ensure that everyone in that society have access to medical care and pharmaceuticals. The United States and Europe have chosen to pass legislation for orphan diseases which require society to spend substantial funds on a limited number of afflicted individuals who suffer from rare diseases. At a global level we would suggest that based on principles of global solidarity, similar efforts should be made to cure neglected diseases which afflict poor people in poor countries. In response, orphan diseases and neglected diseases have been selected as priority diseases, even though the former affect small numbers of patients and the latter affect patients living outside the EU. Special patient
groups (the elderly, women and children) are also considered since these groups often lack effective medicines.

Ethical and moral values are invoked to mobilize support for various health initiatives. There are several schools of moral concepts that have explained this approach. Two are briefly summarized below.

**Utilitarianism** is based on providing the greatest good for the greatest number and is usually defended in terms of efficiency. Across all individuals in a society, the ideal condition is one that maximizes health because health directly generates utility (i.e. generating increased economic growth and, thus, enhancing aggregate income). Therefore, under a strict interpretation of utilitarianism, research funds would be distributed to diseases or specific interventions in such a way as to maximize the net well-being of everyone in the society. The WHO Commission on Macroeconomics and Health estimated the costs and benefits of disease burdens and asserted that investing in health would generate economic growth.\(^4^2\)

**Equity** is a relational concept and much important work has been done to clarify what health equity really is.\(^4^3\) An equity based evaluation should consider not only allocation of a fixed set of health resources, but also the allocation of resources generally between health and other objectives. The basic idea is that burdens (i.e. morbidity, mortality, costs of healthcare) and benefits (i.e. health, well-being, a chance to recover) are distributed fairly across individuals and groups. The equity principle underlies priority setting based on either need, age, or treatment effectiveness. For example, the use of need for priority-setting might rank research into health promotion programs very poorly,\(^4^4\) although from a utilitarian viewpoint, promotion programs might have more “bang for the buck.” Equity remains the presumptive principle in debates over democracy, the social welfare state, and the distribution of income and other goods. Powerful arguments based on equity have been raised, such as the call to expand funding for antiretroviral therapies for people living with HIV and AIDS in poor countries.

**d. Bringing the Evidence Base "Up to date": Modes 1, 2, 5, and 6 in Figure 3.1**

In order to bring these various methodologies up to date, we have used aspects of the framework developed by the Global Forum for Health Research to ask additional questions about the current state of diseases of interest. We have obtained information about the present state of the science, the drug pipelines, and the funds appropriated towards various therapeutic interventions for the conditions identified using our evidence-based approach. Completing the questions highlights the blank areas (i.e. where there are gaps in information needed to make rational decisions).

**e. Priorities based on risk factors: Modes 4-7 in Figure 3.1**

*(For example, smoking, obesity)*

The most critical disease risk factors that will affect the EU countries and the world going forward were selected as the fourth prioritization method along the continuum of Figure 3.1. The answers to these questions are based on data generated by the WHO’s *Global Burden of Disease: 2004 Update* and by the analyses of the more recent and distinct *Global Burden of Disease Study 2010* (see Chapter 4 and associated Background documents). Obesity and smoking are risk factors for major chronic NCDs that influence both length and quality of life. More specifically, obesity and smoking are well-established independent risk factors for...
cardiovascular diseases. While all of these risk factors can and should be addressed through prevention and health promotion activities possible opportunities for pharmacotherapeutic approaches exist. As a result, these risk factors were added to the Preliminary List.

### 6.4 DALYs Burden

A recent study by Catala-Lopez et al examined whether efforts to develop innovative medicines in Europe are focusing on the most relevant conditions from a global public health perspective. The authors reviewed the information on new medicinal products approved by the EU centralized procedure from 1995 to 2009 and evaluated the association between authorized medicinal products and burden of disease measures, based on DALYs in the EU and worldwide. They considered 520 marketing authorizations for medicinal products and 338 active ingredients. There was a positive, high correlation between DALYs and new medicinal product development ($r = 0.619$, $p = 0.005$) in the EU, and a moderate correlation for low- and middle-income countries ($r = 0.497$, $p = 0.030$) and worldwide ($r = 0.490$, $p = 0.033$).

Figure 3.2 shows a plot of the DALY burden of the then EU25 countries versus the proportion of total new chemical entities (NCEs) attributed to that condition. The size of the “bubble” is the weighted fraction of each condition to the total DALY burden. The black line is the 1:1 situation where the fraction (%) of NCEs for that condition matches the proportional DALY burden for that condition. In the EU25, infectious and parasitic diseases, blood and endocrine disorders, diabetes mellitus and genitourinary diseases were all relatively over-represented with regard to NCEs in relation to the disease burden they generate (points above the 1:1 line in Figure 3.2), while the most under-represented conditions were neuropsychiatric diseases, cardiovascular diseases, respiratory diseases, sense organ conditions and digestive diseases (points below the 1:1 line). At the global level (data from the same source, not presented here), the most under-represented conditions were perinatal conditions, respiratory infections, sense organ conditions, respiratory diseases and digestive diseases.
Figure 3.2: Bubble plot representing disability-adjusted life years (DALYs) for EU-25 and active ingredients (NCEs)

Note: The areas of the bubbles are DALYs’ weighted contribution of each disease condition(s) to the total burden of disease. 1: Other neoplasms; 2: Unintentional injuries (poisoning); 3: Congenital anomalies; 4: Digestive diseases; 5: Respiratory diseases; 6: Skin diseases; 7: Respiratory infections; 8: Maternal conditions; 9: Perinatal conditions

7 Conclusions

In this report, four complementary approaches to prioritization are used in an effort to overcome the inadequacies of any one of these approaches when used exclusively. For those decision makers who would like to use only evidence-based approaches, it should be noted that absence of evidence does not necessarily mean there is no threat or need. For those who would prefer to use a consensus-based expert opinion approach, it should be pointed out that such expert groups have often missed important developments. And while an approach based on the use of projections and trends is critical in efforts to prepare for future threats to global public health, it inevitably involves the use of judgments made on the basis of uncertain information. For those who would use social solidarity as the sole criterion for prioritization, it is important to note that there are many people, both rich and poor, from developed and developing countries, who have benefited substantially from medical advances achieved as a result of approaches based on evidence or projections and trends.

In this report a combination of methods have been used to achieve a balanced and optimal result. By using these four approaches together, the health needs of both Europe and the world have been taken into account in addressing pharmaceutical gaps for diseases of current and future public health importance.
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26 WHO IFPMA Working Group , See original Report Appendix 3.7.


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Annex

Annex 3.1: Summary of Reviews on Priority

<table>
<thead>
<tr>
<th>DATE</th>
<th>REFERENCE</th>
<th>PURPOSE/SUBJECT MATTER OF REVIEW</th>
<th>METHOD/SEARCH TERMS</th>
<th>CONCLUSIONS</th>
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<td>2008</td>
<td>Priority Setting Methodologies in Health Research: A workshop convened by WHO's Cluster on Information, Evidence and Research (IER), its Department for Research Policy and Cooperation (RPC) and the Special Programme for Research and Training in Tropical Diseases (TDR)’ World Health Organization, Geneva, April 2008, at <a href="http://apps.who.int/tdr/stewardship/pdf/Priority_setting_Workshop_Summary10_04_08.pdf">http://apps.who.int/tdr/stewardship/pdf/Priority_setting_Workshop_Summary10_04_08.pdf</a></td>
<td>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.</td>
<td>Three main priority setting exercises: Essential National Health Research (ENHR) approach, Combined Approach Matrix (CAM), Child Health and Nutrition Research Initiative (CHNRI) approach</td>
<td>Legitimacy and fairness are the fundamental principles that underlie effective priority setting processes. At the core, priority setting involves adjudicating between a wide range of values, some of which conflict, including: benefit, evidence, cost, efficiency, equity, equality, benefit to a country’s economy, severity of disease, prevalence of disease, solidarity, protection of the vulnerable, and more.</td>
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To review studies that empirically analyse a macro- and meso-level decision-making process for including drugs in and/or excluding drugs from reimbursement lists and drug formularies in industrialized countries.

MEDLINE was searched from 1990 to February 2007 with the following keywords: “pharmaceutical preparations” or “pharmaceutical services” or “pharmacy and therapeutics committees” or “pharmacy administration” or “formularies” or “drug costs” or “drug approval” and “health care rationing” or “health priorities” or “health policy” or “policy making” or “decision-making”.

Final tally: Six original research articles. Three of those six studies were conducted in Canada, and the rest in the United Kingdom, France and Finland. The clinical evidence on benefit and the quality of that evidence were the main criteria used in priority setting concerning medicines. In some cases the clinical benefit was explicitly divided into efficacy and adverse effects. The costs of the drug emerged as the second major criteria in the decision-making. Cost containment and keeping the budget balanced is supposedly in the background of every decision-making system explored in the studies. However, only one study indicated that the decision-makers had a predefined amount of money to cover drug expenses, which explicitly sets cost as an important criterion in decision-making. Formal pharmacoeconomic analyses had a rather minor role in decision-making. The majority of the studies concentrated on descriptive analysis on how things are rather than on explicitly analysing how decision-making processes perform against some defined principles or goals.
### 2009


To identify and stimulate research most likely to reduce global newborn infection-related mortality by 2015.

The Department of Child and Adolescent Health and Development of the World Health Organization (WHO/CAH) applied the Child Health and Nutrition Research Initiative (CHNRI) priority-setting methodology. Technical experts systematically listed and then used standard methods to score research questions according to their likelihood to (i) be answered in an ethical way, (ii) lead to (or improve) effective interventions, (iii) be deliverable, affordable, and sustainable, (iv) maximize death burden reduction, and (v) have an equitable effect in the population. The scores were then weighted according to the values provided by a wide group of stakeholders from the global research priority-setting network.

On a 100-point scale, the final priority scores for 69 research questions ranged from 39 to 83. Fifteen research questions received the highest scores, most were in the domain of health systems and policy research to address barriers affecting existing cost-effective interventions. The priority questions focused on promotion of home care practices to prevent newborn infections and approaches to increase coverage and quality of management of newborn infections in health facilities as well as in the community.

### 2009

**Setting priorities for health interventions in developing countries: a review of empirical studies, *Tropical Medicine & International Health* 14(8): 930–939 (2009) Youngkong et al.**

To assess and summarize empirical studies on priority-setting in developing countries.

Medline and EMBASE (Ovid) databases: ‘health’ and ‘priority-setting’ or ‘prioritization’ or ‘resource allocation’, in combination with the names of developing countries according to World Bank (2008) definitions.

A total of 18 studies were finally selected. All studies were published after 1999; and 13 in the period 2006–2008. 13 studies primarily aimed at identifying criteria for setting priorities in health care. Three studies explored the acceptability of using economic evaluation or burden of disease information in decision-making health priorities. One study examined the introduction of ‘Accountability for reasonableness’ to improve the priority-setting process and one study described the

Literature review and an analysis of health research priority setting exercises that were organized or coordinated by the World Health Organization since 2005, checklist for health research priority setting that allows for informed choices on different approaches and outlines nine common themes of good practice.

(search terms: (setting priorities [title/abstract] OR priority setting [title/abstract]) AND research [title/abstract]). Additionally, the World Health Organization (WHO) library database (WHOLIS) was sought for literature emanating from WHO on this topic (search terms: (research AND priorities) OR (research AND priority) OR (research AND agenda)). Second, health research priority setting exercises that were organized or coordinated by WHO headquarters since 2005 were reviewed. Documents describing these exercises were identified through the search of WHOLIS and by a manual search of all departmental websites of WHO. Methods used for prioritizing research were analysed in the 230 documents that were found. Finally, a process of expert consultation was employed using in-depth and semi-structured interviews with staff in WHO and a selection of international research organizations experienced in health research priority setting.

Nine common themes for good practice in health research priority setting (i.e. elements of a health research priority setting process that are key and should not be overlooked) emerged and were combined into a checklist for health research priority setting (See Table 1 of this document: ANNEX).
<table>
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<th>Year</th>
<th>Title</th>
<th>Details</th>
<th>References</th>
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<tr>
<td>2010</td>
<td>Evidence-Based Priority Setting for Health Care and Research: Tools to Support Policy in Maternal, Neonatal, and Child Health in Africa, PLoS Med 7(7): e1000308. 10.1371/journal.pmed.1000308, Rudan I, Kapiriri L, Tomlinson M, Balliet M, Cohen B, Chopra M.</td>
<td>To present the available tools for priority setting that could be used by policy makers in low-resource settings. An assessment of the applicability and strengths of different tools in the context of maternal and child health in sub Saharan Africa.</td>
<td>16 references found: No explicit search methodology</td>
</tr>
<tr>
<td>2011</td>
<td>Critical shortage of new antibiotics in development against multidrug-resistant bacteria—Time to react is now, Drug Resistance Updates 14 (2011) 118–124, Freire-Morana L, Aronsson B, Manz C, Gysens IC, So AD, Monnet DL, Cars O., The ECDC-EMA Working</td>
<td>Summary of the status of the antibacterial drug development pipeline, with attention to new agents that have entered clinical development, especially antibacterial agents for systemic administration.</td>
<td>Two commercial databases (Pharmaprojects and Adis Insight R&amp;D) were queried for antibacterial agents in clinical development. For each agent, reviewers were requested to indicate whether its spectrum of activity covered a set of selected multidrug-resistant bacteria, and whether it had a new mechanism of action or a new target. In addition, PubMed was searched for antibacterial agents in development that</td>
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Broadly, there are three categories of research that has been performed on research priority setting at WHO. Firstly, analysis of research priority setting practices at WHO, secondly normative work, attempting to provide guidance on research priority setting, and thirdly research priority setting exercises themselves that have performed research on methodologies for research priority setting as preparatory work. There is "... currently insufficient evidence that the use of priority-setting tools improves health outcomes and reverses existing inequities... we have ample evidence that the lack of a rational and transparent process generates inequity and stagnation in mortality levels."

90 agents were considered to fulfil the inclusion criteria for the analysis, 66 were new active substances. Fifteen of these could be systemically administered and were assessed as acting via a new or possibly new mechanism of action or on a new or possibly new target. Out of these 15, 12 agents were assessed as having documented in
Update on 2004 Background Paper, BP 3 Approaches to Priority Setting

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<tr>
<td>2012</td>
<td>From efficacy to equity: Literature review of decision criteria for resource allocation and healthcare decision making, <em>Cost Effectiveness and Resource Allocation</em> 2012, 10:9 doi:10.1186/1478-7547-10-9, Guindo et al.</td>
<td>To identify decision criteria and their frequency reported in the literature on healthcare decision making.</td>
</tr>
</tbody>
</table>

MEDLINE and EMBASE: The optimized search strategy included the following keywords: “decision-making”, “priority-setting”, and “resource allocation”, combined with “funding”, “budget”, “cost-benefit analysis”, “cost-effectiveness analysis”, and “equity”.

The most frequently mentioned criteria were: equity/fairness (32 times), efficacy/effectiveness (29), stakeholder interests and pressures (28), cost-effectiveness (23), strength of evidence (20), safety (19), mission and mandate of health system (19), organizational requirements and capacity (17), patient-reported outcomes (17) and need (16).


vitro activity against antibiotic-resistant Gram-positive bacteria and only four had documented in vitro activity against antibiotic-resistant Gram-negative bacteria. Of these four, two acted on new or possibly new targets and, crucially, none acted via new mechanisms of action.
Appendices

App 3.1 Health research prioritization at WHO; An overview of methodology and high level analysis of WHO led health research priority setting exercises, 2010. WHO

App 3.2a PRESS RELEASE; EMEA concludes first accelerated assessment for a medicine for human use, 2007. European Medicines Agency

App 3.2b COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) GUIDELINE ON THE PROCEDURE FOR ACCELERATED ASSESSMENT PURSUANT TO ARTICLE 14 (9) OF REGULATION (EC) No 726/2004. European Medicines Agency


App 3.3b 53rd Meeting of the ACHR, 2010. Advisory Committee on Health Research


App 3.3d Priority Setting Methodologies in Health Research; A workshop convened by WHO's Cluster on Information, Evidence and Research, 2008. WHO

App 3.3e Global strategy and plan of action on public health, innovation and intellectual property, 2008. WHO


App 3.3g Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination, 2012. WHO

App 3.3h Global Health Policy Forum , 28 June 2012; Rue de la Science 15/NYERERE, 1049 Brussels.


App 3.5a The Innovative Medicines Initiative (IMI) Research Agenda; Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society, 2008.

App 3.5b The Innovative Medicines Initiative (IMI) Scientific Research Agenda; Revision 2011.

App 3.5c The Innovative Medicines Initiative (IMI) Annual Implementation Plan 2012