3. Approaches to priority setting

See Background Paper 3 (BP3_Approaches.pdf)

3.1 Introduction

This chapter reviews the various approaches which have been used to set priorities for health research — both at the international and national level — and explains the rationale for the choice of methods used in this Project (see 2004 Report, Background Paper 3 and present Report, Background Paper 3). The key message underlined in the 2004 Report and reiterated here is that all methods of priority setting have limitations and that different methods need to be used, depending on the particular circumstances. A combination of methods has therefore been used in this Report.

Priority setting is a challenge at all levels (global, national and local) and for all contexts in health systems. Both consumers and funders are demanding greater accountability for how limited health resources are used to meet health system goals. As a result, public and private sector research funders have to make difficult decisions about which fields and specific studies to support.

However, there is virtually no consensus regarding which, or whose, values should guide decisions about allocation of research funding and how these values should inform priority setting. In short, there is no “best practice” (see Viergever et al. 2010. A checklist for health research priority setting and Appendix 3.1).

There are two broad approaches to setting priorities for health research: the use of technical analyses, which rely on quantifiable epidemiologic, clinical, financial or other data; and the use of 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 measurable units such as diseases (burden of disease) or interventions (with respect to their costs and use). 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 health care services. 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 United States National Institutes of Health (NIH), the Science and Technology Council of Australia, or even large pharmaceutical companies.
3.2 Conceptual framework for the Priority Medicines Project

The conceptual framework for this updated 2013 Report has not changed. The Project used different methods from the spectrum of possible approaches: evidence-based approach (burden of disease and mortality data); future projections approach; risk factor approach; and social solidarity approach. A framework for this kind of analysis has been developed by the University of Colorado in the United States (see Figure 3.2.1).

Figure 3.2.1: A cognitive continuum framework

![Cognitive Continuum Framework](image)


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3.3.1 Overview of the literature post-2004

There have been several literature reviews in this fairly active area since 2008. Reports have evaluated priority setting against an ethical framework. The factors that impact priority setting have been studied as well, such as amount and type of stakeholder engagement, cultural factors supporting explicit priority setting, decision maker/group composition (size and clarity of process, local ownership and awareness and representation), and management of local politics. These are summarized in Background Paper 3. A key conclusion of this review for the present updated report is
that there is still very little information on how **funding** decisions are developed for biomedical research.

### 3.3.2 Defining a priority medicine: the role of regulatory authorities

The regulatory authorities of the EU, Canada and the United States determine whether a medicine should be a “priority” for regulatory purposes. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have established categories of medicines, based on whether or not they demonstrate improvement over existing medicines. Such a designation facilitates the registration process. Although not intended for use in prioritizing research, in practice this designation is intended to reward successful research (see Background Paper 3).

#### European Union

In November 2005, one year after the publication of the 2004 Priority Medicines Report, accelerated assessment was introduced by revised EU pharmaceutical legislation. 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 although if major objections to this are uncovered during the assessment, the timing is reverted to the normal timetable for the centralized procedure, which allows a maximum assessment period of 210 days. In 2007, the medicinal product, eculizumab, from Alexion Europe SAS, was the first medicinal product for which an accelerated assessment procedure was concluded successfully.

Two other pathways to address ‘unmet medical needs’ are the conditional approval and the exceptional approval pathway. In case of conditional approval, marketing authorization is granted based on a smaller package of clinical data, with follow-up obligations to submit additional clinical efficacy and safety evidence of the product. For some products, such as certain orphan medicinal products for extremely rare diseases, it will usually never be possible to assemble a full dossier. These products may be approved under an ‘exceptional approval’ scheme, without further post-approval obligations.

#### The United States

The classification system of the FDA assigns all new drug approvals to categories representing distinct levels of innovation, and this classification is of particular relevance here as it highlights the different meanings of the term *innovation*. The FDA reviews new drug applications (NDAs) and awards **priority** status based on chemical type and therapeutic potential. With regard to the latter, a drug qualifies for **priority review** if it offers a potentially 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 USA market. An incrementally
**modified drug (IMD)** is one that relies on an active ingredient present in a drug already approved for the USA market (or a closely related chemical derivative of such an ingredient), and has been modified by the manufacturer. Drugs are classified as **other** if they rely on 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 it can be a NME, IMD or other. Most United States observers 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.13

The FDA’s **fast track** process is designed to facilitate the development, and expedite the marketing review, of drugs that both target “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 which may be potentially superior to existing therapy. If there are existing therapies, a fast track drug must show some advantage over available treatment, such as: 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 the 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. A drug that receives “fast track” (and probably also priority review) designation is eligible in effect for more frequent contact with the FDA as well as eligibility for a third component of prioritisation, “accelerated approval” i.e., marketing approval on an effect on a surrogate, or substitute endpoint reasonably 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.

Another FDA initiative, **priority review vouchers** are, in essence, a prize incentive for companies to invest in new drugs and vaccines for neglected tropical diseases. A provision of the Food and Drug Administration Amendments Act (HR 3580) awards a 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, also entitles the bearer to a priority review for another product.
3.4 Public sector priority setting for research and development

The United States National Institutes of Health (NIH), the largest public funder of biomedical research in the world, has identified five criteria that play a critical 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 (since it is impossible to predict exactly where advances will occur); and (5) national training and infrastructure needs. The first of these criteria, public health needs, is determined on the basis of five considerations: the number of people with a specific disease; the number of deaths attributable to a specific disease; the degree of disability caused by a specific disease; to what extent a specific disease shortens the average human lifespan; the financial and social costs of a specific disease; and threats posed to others by contagious disease. According to the NIH in 1997, these five considerations for determining “public health needs” were of equal importance in allocating research resources.\(^\text{14}\)

At the time of the 2004 Report, only four institutes of the NIH - the National Cancer Institute (NCI), the National Institute of Child Health & Human Development (NICHD), the National Institute on Aging (NIA) and the National Institute of Environmental Health Studies (NIEHS) - had the facility to retrieve bibliometric data to track the publications and assess the potential public health impact of their grantees. Of these, three institutes (NIEHS, NICHD and NIA) have collaborated to develop a database to improve the priority-setting process.\(^\text{15}\) The Office of Portfolio Analysis (OPA) was only recently established in 2011 by the NIH as a whole 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.”\(^\text{16}\)

With regard to the practical output of awarding NIH grants, there is still inadequate linkage between NIH awards and literature/citation data. Some preliminary bibliometric analysis suggests that the effect of a publication’s “impact factor” is more predictive of the fate of R01 grants than the number of subsequent citations of the investigators. At a Portfolio Analysis Workshop in July 2012, a survey of over 500 participants showed that 47% thought that measuring the impact of NIH grants would be the most important task in the work of the OPA.\(^\text{16}\)

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 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 (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 (see 2004 Report, Chapter 3 Appendix 3.1).
The Essential National Health Research (ENHR) 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.\(^{17}\)

The World Development Report (1993) was produced by the World Bank in conjunction with the WHO and used a key measure of the burden of disease and disability called the Disability Adjusted Life Year (DALY), which has also been used in this Project (see Background Paper 4).\(^{18}\)

The Ad Hoc Committee on Health Research (1996) was established in 1994 by the WHO. It identified a systematic “five-step” process which is the basis of the conceptual model used in this project.\(^{19}\) Briefly, these five steps include: 1. Calculate the burden of the conditions or risk factor (look at the magnitude); 2. Identify the reason why the disease burden persists (look at determinants); 3. Judge the adequacy of the current knowledge base (assay knowledge); 4. Assess whether new R&D would improve population health and at what cost (understand cost and effectiveness); 5. Assess the adequacy of the current level of effort.

The Global Forum for Health Research (2000) created a framework (Combined Approach Matrix) which brings together in a systematic manner all information (current knowledge) related to a particular disease or risk factor\(^{20}\) (see 2004 Report Chapter 3, Appendix 3.6).

WHO-IFPMA Round Table (2000-2001) was a joint task force, comprising representatives of the WHO and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), convened to establish a working list of infectious diseases and to review disease burden as a way of directing research priorities. The task force also used additional criteria such as mortality, societal costs, likelihood of treatment, and future trends. (See 2004 Report Chapter 3, Appendix 3.7).

The UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR) prioritized research by using an adapted version of the Global Forum’s framework for priority setting, expanded to include information on the comparative advantages of the TDR.\(^{21}\) (See 2004 Report Chapter 3, Appendix 3.4).
3.5 Approaches to priority setting post-2004

Priority Setting Methodologies in Health Research (2008) was the theme of a workshop held at the WHO in Geneva, Switzerland in April 2008. The overall 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 Background Paper 3 and Annexes).

The Child Health and Nutrition Research Initiative (CHNRI) (2007) 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.22,23

3.6 Private sector prioritization methods

Methods of prioritization in the pharmaceutical industry vary from company to company depending on their history and strategic vision. Decisions about new medicines are generally made within a set of four different contexts: scientific opportunity, market assessment, available and required resources, and medical need. The common steps taken are to:

- Review the marketplace to identify unmet medical needs.
- Benchmark competitor products to understand the competitive landscape.
- Identify the market segments and patient populations a product will target.
- Identify all possible additional indications that might make the compound more valuable.
- 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. The goal of market research at this point would be to find a product profile which payers are willing to pay for and which provides a sufficient return on investment (for example, is the product profile such that physicians would prescribe it at the levels needed to justify further development?).
- Assemble market research to profile key geographic markets to ensure product success.
The strength of this approach is that it clearly identifies products that the "market" is willing to pay for and that will ensure an adequate return on investment. Unfortunately, this approach will ignore diseases which mainly affect the poor in low-income countries.

3.7 Prioritizing for the Priority Medicines Project

An assumption in the methods used in this report is that the higher the disease burden, the greater the cost to society of the disease, and 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, ranging from epidemiologic measures to combinations of mortality and morbidity (such as the Disability Adjusted Life Year (DALY)). A version of this approach is used in the present method (see Background Paper 4).

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 3.7.1 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 (see Catalá-López et al. Population Health Metrics, 2010).

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 3.7.1), 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.
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Figure 3.7.1: 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

3.8 Providing a menu of complementary priority setting approaches

As in the 2004 Report, the present report uses several complementary approaches for establishing priorities for biomedical research. Where adequate data are available on burden of disease and on the efficacy or lack of efficacy of treatments, an evidence-based approach has been used (Modes 1-2 in Figure 3.2.1). Where data on burden of disease or efficacy do not exist, projection or trend analysis methods have been used (Modes 4-6 in Figure 3.2.1). For rare diseases and neglected diseases or where market failures occur, principles of social solidarity have been applied (Modes 4-7 in Figure 3.2.1). (See Background Paper 3). Where it is clear that risk factors play a role in the development of multiple disease states (mainly noncommunicable diseases), risk factors (obesity, smoking) have themselves been used as a priority condition (Modes 4-7 in Figure 3.2.1).

In order to bring complementary information to this approach, the framework developed by the Global Forum has also been used to ask additional questions about the current state of diseases of interest. This framework can be seen in the templates developed for determining pharmaceutical gaps in Chapter 6. As these are different though complementary methods the outcomes of each approach cannot be directly
compared. All four approaches have been presented to give a comprehensive overview of “pharmaceutical gaps” that can be prioritized for research.

### 3.8.1 Priorities based on evidence-based approach
(For example, acute stroke, chronic obstructive pulmonary disease (COPD), Alzheimer disease: Modes 1 and 2 in Figure 3.2.1)

For this approach, burden of disease analysis has been used to determine a preliminary list of high burden diseases and conditions. The combination of burden of disease and clinical efficacy provides a preliminary list of conditions which have pharmaceutical gaps (see also Background Paper 5).

### 3.8.2 Priorities based on projections and trends
(For example, antimicrobial resistance (AMR), pandemic influenza: Modes 4-7 in Figure 3.2.1)

Looking ahead, what are the emerging diseases that could affect the EU and the world? The answers to these questions form the second prioritization method and are based primarily on consensus judgements and observational and clinical evidence. Although AMR is not a disease or condition *per se*, its importance as a threat to global public health is expected to continue to grow. The same holds true for pandemic influenza.

### 3.8.3 Priorities based on social solidarity
(For example, rare or neglected diseases: Modes 4-7 in Figure 3.2.1)

The ethical and moral aspects of priority setting have been selected as the third prioritization method along the continuum of Figure 3.1. Ethics and moral values are often invoked to mobilize support for various health initiatives, and theories of social justice (for example, the fair and equitable treatment of people) have been applied to justify medicine and public health as a special "social good" (see 2004 Report, Background Paper 3). Many European countries have a long history of social solidarity. This has been demonstrated by the creation of universal social security systems and of national health systems which are intended to ensure universal access to medical care and pharmaceuticals.

In the EU and elsewhere, governments have enacted legislation to protect the interests of people suffering from rare (“orphan”) diseases. This requires society to spend substantial funds on a limited number of people who suffer from rare diseases. At a global level, based on principles of global solidarity, similar efforts are needed to address neglected diseases, which mainly affect the poor in low-income countries, as well as other poor populations. 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.
3.8.4 Priorities based on risk factors
(For example, smoking, obesity: Modes 4-7 in Figure 3.2.1)

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 3.2.1. 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 tobacco use are risk factors for major chronic noncommunicable diseases (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.

3.9 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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