4. Methods used in the Priority Medicines Project

See Background Paper 4 (BP4_Methods.pdf)

4.1 Introduction

The methodology described in this chapter is designed to determine pharmaceutical gaps and to create a public-health-based research agenda for the European Union (EU). This Project has combined a number of methods to produce a methodology that can be used for priority setting at country, regional and global levels. The method is intended to be explicit and reproducible (source data are provided on the WHO website). This chapter provides details of the four complementary approaches used: the evidence-based approach; future projections approach; the risk factor approach; and the social solidarity approach. (See Background Paper 4).

4.2 Applying the methodology

The methodology involves the use of analyses of several different factors: demographics, burden of disease and clinical efficacy.

1. The first step was a review of demographic factors (such as life expectancy and age distribution) for countries in Europe (including the EU27) and the world to set the context for the Report.

2. A ranking exercise was then carried out, using burden of disease information (Disability Adjusted Life Years (DALYs) and mortality), to generate two lists: one list of the major diseases and conditions which account for the majority of the total DALY burden in both the EU 27 and the rest of the world; and the second a counterpart list for the total mortality burden of major diseases and conditions (see Chapter 5, Tables 5.3 and 5.4). These are called the burden of disease and mortality lists in Figure 4.1 below.

3. Some of the conditions on these lists, such as road traffic accidents, were then excluded, mainly because pharmacotherapies were not amenable to deal with these conditions.

4. Additional criteria derived from the three other approaches (Section 4.7) were then applied to generate additions to the diseases and conditions on these two lists. These included: health-related projections and trends; risk factors; and social
solidarity/social justice/equity. The Primary List was then generated by combining the DALY and mortality lists, removing any duplicate conditions, and adding new ones based on the three additional approaches (Figure 4.1).

5. A series of background papers were then commissioned for each of the conditions identified on the Preliminary List. These are the in-depth reviews referred to in Figure 4.1. Each reviewer was asked to format the background paper according to a template described in more detail in section 4.9. They were also asked to review the Cochrane Database of Systematic Reviews to determine whether the pharmaceutical interventions available to treat these Preliminary List diseases were efficacious. Information on diagnostics and vaccines was also included, where appropriate. The purpose of these in-depth reviews was to determine whether a pharmacotherapeutic treatment gap existed in any of the selected conditions. The detailed Background Papers are summarized in Chapter 6.

6. The diseases and conditions on the Preliminary List identified as having pharmaceutical gaps were then added to the Final List, as shown in Figure 4.1. Key aspects of the methodology are discussed in more detail below.
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Figure 4.1: Schematic of the methodology used in the Priority Medicines Report

- Burden of disease and mortality ranking
- Burden of disease list and mortality list
- Apply exclusion criteria
- Preliminary List of Diseases (Chapter 5)
  - IN-DEPTH REVIEWS OF PRELIMINARY LIST USING TEMPLATE: "GAP" ANALYSIS (Chapter 6)
    - Template (BoD review, market and "pipeline" analysis)
    - Cochrane Reviews and/or BMJ Clinical Evidence
- Is there a "Pharmaceutical Gap"?
  - Can we bridge this gap?
- Final List of Priority Conditions/Diseases
  - Chapter 9 Conditions/Diseases
4.3 **Sources of data: Demographic**

The demographic component of this report is based on important regional and international reports and databases in which the following parameters were analysed: life expectancy at birth; age distribution of the world population; fertility rates; and distribution of people living in urban and rural areas. The primary database used was the World Development Indicators database¹ (see Background Paper 5).

4.4 **Geographical Definitions**

In some parts of this report, data on the EU 27 countries (listed below) is used as well as on subunits of the EU27, depending on when various countries joined the EU.

**EU 27:** As of 2013, the 27 Member States of the European Union are Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

Where data on the 27 individual EU countries was not available, data on the WHO European Region was used. This was the case, for example, for the DALY statistics used, which were based on the 2008 estimates from the WHO Global Burden of Disease Database. The WHO European Region comprises over 50 countries, including the EU27, and covers a vast geographic region, from Iceland to Kazakhstan.

While the WHO Global Burden of Disease 2004 bases data for Europe on the WHO European Region, the GBD 2010 study provides differentiated data for three European sub-regions (established on the basis of epidemiological homogeneity and geographic contiguity). A total of 21 regions were created globally, of which three are relevant to the European countries:

1) **Central Europe:**
Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, the former Yugoslav Republic of Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia.

2) **Eastern Europe:**
Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation, Ukraine.

3) **Western Europe:**
Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.
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4.5 Sources of data: Burden of disease

4.5.1. Disability Adjusted Life Years (DALYs)

Over the past these decades, the WHO, the World Bank and many other organizations have used and promoted the concept of DALYs as an integrated measure of mortality and disability. The indicator combines mortality and morbidity in a single measure. One DALY can be thought of as one lost year of ‘healthy’ life and the burden of disease as a measurement of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability. In brief, DALYs are a way of aggregating the number of life years lost by sufferers from each disease with the amount of disability suffered while they are still alive. These two amounts are combined in a complex manner to give the overall burden of that disease. Disease burdens are thus measured in DALYs lost due to each disease. This burden of disease approach can be broken down to show the relative contributions of different conditions to the overall burden of disease and it can show the burden of disease that can be attributed to known risk factors.

Although the DALY methodology is not perfect, it is the best single tool available for the intended audience of this report (i.e. strategic planners and decision makers). It provides a single summary measure of ill health, a fundamental tool for policy makers when considering the relative benefits of different policy options (see Background Paper 1.3).

Measuring the burden of disease using DALYs is well-established. It can be broken down to show the relative contributions of different conditions to the overall burden of disease; it can show the burden of disease that can be attributed to known risk factors; and can be combined with cost to assess cost-effectiveness. In calculating DALYs, this Report uses projections for 2008 for the EU27 and the world, obtained from the WHO Global Burden of Disease Database.²

In late 2012, a new study on worldwide burden of disease was published: the Global Burden of Disease Study 2010 (GBD 2010). This study was not an update of the WHO’s The Global Burden of Disease: 2004 Update, but a new collaborative global burden assessment exercise, which includes a more extensive set of disease sequelae, age groups and regions.³ ⁴

The GBD 2010 analyses differ in several ways from those of the WHO Global Burden of Disease 2004 (see Background Paper 4). For example, in the GBD 2010 Study, death rates and numbers have been estimated with 95% uncertainty intervals (95% UIs). In Chapters 5 and 6, the most recent 2010 data has been presented in addition to the 2008 projections.
4.5.2 Mortality

Mortality is also used here as a measure of burden of disease as this is easy to understand. However, this measure is not able to reflect the burden of pain and suffering experienced by patients with chronic diseases such as osteoarthritis. The mortality data used here are actual (not estimated) data for 2008 from the WHO Global Burden of Disease Database which estimates global and regional mortality. These data have been disaggregated into broad categories and then into specific disease categories and are made available by country, sex and age group. The GBD 2010 Study also provided mortality data.

4.6 Applying exclusion criteria to the Burden of Disease and Mortality List

Once the burden of disease and mortality lists had been generated, the next step was to eliminate conditions and diseases that, based on our experience and literature review, that could not be cured or treated with pharmaceutical interventions designed for the specific condition. These were: intentional and unintentional injuries; road traffic accidents; refractive errors; birth trauma; and childhood cluster diseases.

4.7 Considerations to generate additions to the Preliminary List.

Several other domains or factors were analysed in order to identify other diseases and conditions that should be added to the Preliminary List. These were risk factors based on analyses carried out as part of the WHO Global Burden of Disease 2004 study; social solidarity; and future trends and projections (demographic and epidemiological).

Approach based on risk factors

Substantial proportions of global disease burden are attributable to major risk factors. In both developing and high-income countries, leading risk factors such as smoking, alcohol consumption and obesity account for a large burden of disease. Prevention strategies that target these known risks can provide substantial and underestimated public health gains. For this reason, risk factors were added to the list of conditions and diseases used to generate the Preliminary List (Figure 4.1).

Approach based on projections and trends

As in the 2004 Report, diseases that will affect the EU countries and the world were reviewed. What existing diseases will grow in importance? The answers to these questions form another prioritization method and are based primarily on consensus judgements and observational and clinical evidence. In addition, resolutions of the WHO World Health Assembly (WHA) and the European Parliament have identified antimicrobial resistance (AMR) as a serious threat to global public health.
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Approach based on social solidarity

Again as in 2004, another approach used concepts of social justice, social solidarity and equity to place on the Preliminary List certain conditions with pharmaceutical gaps, such as rare (orphan) diseases and neglected tropical diseases. Diseases affecting special patient groups (the elderly, women and children) are also included (see also Background Papers 7).

4.8 Generating the Preliminary List

Based on the three considerations outlined above, pharmaceutical interventions dealing with obesity and smoking (risk factors), those for AMR and influenza (epidemiologic projections) and those for rare (orphan) diseases and neglected tropical diseases (based on social solidarity concerns) were added to the list together with the disease burden “league tables” to create a Preliminary List of Diseases (see Chapter 5 and the associated Background Papers).

4.9 Background reviews

In-depth or background reviews of each of the Preliminary List entities were based on the Global Forum for Health Research approach. The diseases and conditions identified in the Preliminary List were rigorously reviewed by asking the following questions:

- What is the size and nature of the disease burden?
- What is the control strategy? Is there a pharmaceutical gap?
- Why does the disease burden persist?
- What can be learnt from past/current research into pharmaceutical interventions for this condition?
- What is the current “pipeline” of products that are to be used for this particular condition?
- What are the opportunities for research into new pharmaceutical interventions?
- What are the gaps between current research and potential research issues which could make a difference, are affordable and could be carried out in a) five years or b) in the longer term?
- For which of these gaps are there opportunities for pharmaceutical research?

This is the same set of questions posed in the in-depth reviews in the 2004 Priority Medicines Report. Based on these specific reviews, opportunities to close existing pharmaceutical gaps have been identified for each condition.
4.10 Background reviews: clinical efficacy

A prerequisite for the in-depth reviews was to have a measure of the clinical efficacy of the different pharmaceutical interventions currently available. The primary data source used for this was the collection of analyses in the Cochrane Database of Systematic Reviews. The reviewers also used the Clinical Evidence summaries of the British Medical Journal which present information in a less quantitative format. The Cochrane systematic reviews, based on relevant studies from the international medical literature, are conducted by the international Cochrane Collaboration, an organization of over 7,000 health professionals, researchers, scientists and consumers from approximately 80 countries. There are 50 international Cochrane Review Groups. These highly structured reviews summarize and synthesize results from the highest quality research studies, usually randomized, placebo-controlled trials. The results are combined statistically.

The work of the Cochrane Groups is considered the gold standard in the search for the best systematic reviews of medical evidence. However, the Cochrane Database has a number of limitations. One of the drawbacks is that these reviews are retrospective. As a result, the most recent interventions or products without market approval may not have sufficient numbers of patients or trials to warrant a systematic review. Moreover, some of the interventions that are reviewed may no longer be used in clinical practice or have been superseded by other, more effective interventions.

Another drawback is that most trials data in the Cochrane Database are randomized placebo-controlled trials and do not include other data such as that from observational studies (see also Chapter 8.4). Where possible, decisions should be based on comparison of new interventions with current practice, not with placebos. What is important from a public health viewpoint is not whether a new intervention works better than “nothing”, but whether it works better than the current best available treatment.

Another limitation of the Cochrane Database is the limited data on adverse events – information which may be useful in determining R&D priorities. The randomized clinical trials in the database are designed to assess efficacy and only occasionally report side-effects. Analyses of the available data on adverse events from the Cochrane Database were not used in determining priorities because only a small number of trials were involved. The difficulty faced in obtaining this data underlines the need to improve the regulatory process using Phase IV research (post-marketing surveillance) to collect data on both adverse events and exposure to pharmaceuticals in large numbers of patients.

**Measures of clinical efficacy**

Clinical efficacy is a measure of the accuracy or success of a diagnostic or therapeutic technique when carried out in a clinical trial. The Cochrane Reviews should be viewed in terms of clinical efficacy and not clinical effectiveness, the latter defined as the
accuracy or success of a diagnostic or therapeutic technique when carried out in a “real-world” clinical environment. That is, clinical effectiveness is the extent to which a treatment achieves its intended purpose. In the present Report these terms are not used interchangeably and the reader should be aware of this distinction.

The Cochrane system uses different statistical measures for summarizing the results of a large number of placebo-controlled clinical trials. In order to display all of the data in a consistent way, the results from the original Cochrane tables of results have been reviewed to extract the Relative Risk (RR) and Odds Ratios (ORs) and other measures. This involved the use of revising the existing pooled mean estimates of the Relative Risk and Odds Ratios from the existing Cochrane analyses comprising the same intervention so that desired (i.e. beneficial) outcomes have ratios greater than one. This is not necessarily the normal manner of presentation as, depending on the outcome measurement, beneficial outcomes may have Relative Risk or Odds Ratios less than one. Nonetheless, where appropriate, these transformations make it possible to display the results graphically in a way in which treatment effects better than placebo fall above the horizontal line.

As an example, Figure 4.2 shows the results obtained from many trials of different treatments for heart attacks (myocardial infarction). The mean Relative Risk and/or Odds Ratios derived from many trials for each intervention are displayed as square boxes in the vertical lines. These vertical lines represent “95% confidence intervals.” This means that if the trials comprising the pooled results were repeated by re-sampling 100 times, in 95 of the 100 times, the true value for the mean Relative Risk and Odds Ratios would fall somewhere along the vertical line.

Where the square box is above the horizontal “1” line but the confidence interval line crosses below the horizontal “1” line this means that the benefits shown by the various clinical trials for the particular intervention might have occurred by chance alone. Therefore, in the statistical sense, the intervention has not been shown to have an unequivocal benefit. Figure 4.2, shows that in many trials the intervention was more clinically efficacious than the placebo as the lower boundary of the confidence interval is above the horizontal “1” line.

In the Background Papers of Chapter 6, a number of these charts are used to show where pharmaceutical gaps have been identified by using this methodology. Although these particular Cochrane-generated figures may mix different treatments and outcomes, it is striking how, for some conditions, nearly all the pooled trial results consistently demonstrate efficacy, while others, consistently fail to demonstrate efficacy.

The methods described in this chapter are detailed in the Background Papers and associated Appendices and Annexes. The original burden of disease databases and the

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1 Most confidence intervals involving ratios are asymmetric so the Relative Risk ratios are not in the middle of each vertical line.
spreadsheets of the Cochrane Database analyses are available on the website to enable review of the results and further analyses for different countries or regions.

**Figure 4.2: Trial results for different myocardial infarction treatments**

<table>
<thead>
<tr>
<th>Outcome: mortality or myocardial infarction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
</tr>
<tr>
<td>13.21</td>
</tr>
</tbody>
</table>

RR or OR <1 favours the intervention (less mortality or myocardial infarction).

### 4.11 Data sources for R&D funding

Donors interested in funding R&D of products for neglected diseases 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, patchy and 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 to better target their investments into neglected disease product R&D. G-FINDER tracks global investment annually in
this area. It is hoped that by providing funders with better information, the G-FINDER survey will 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, including medicines, 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.

4.12 Conclusions

The methodology described above serves as the basis for determining priorities for a public-health-based research agenda for the EU. This is accomplished using in-depth analyses to decide which pharmaceutical gaps warrant further study. As discussed in Chapter 3, the prioritization scheme employs several different conceptual frameworks. The "ethical/moral" conceptual framework for prioritization is summarized in Chapter 3. The "evidence-based" framework, which is described in more detail in this Chapter, combines burden of disease and risk factor analysis with clinical efficacy measurements. This is further updated by informed judgments about future clinical and epidemiological scenarios and by in-depth (Background) reviews of recent science, drug development and market analyses for multiple disease areas.

References


8 The Cochrane Library, from the Cochrane Collaboration. Available at [www.thecochranelibrary.com](http://www.thecochranelibrary.com).
9 BMJ Clinical Evidence reviews. Available at http://clinicalevidence.bmj.com/x/index.html.

10 G-FINDER. Available at http://g-finder.policycures.org/gfinder_report