9. Summary of observations, discussion, conclusion and recommendations

9.1 Introduction

The 2004 Report *Priority Medicines for Europe and the World* determined the priority needs for pharmaceutical innovation from a public health perspective and made policy and research recommendations to address these needs. Within this public health context, a key objective throughout the 2004 Report has been the need to identify common areas of interest between Europe and the world as a whole, particularly in the area of discovering and developing new and improved medicines to combat diseases and conditions which pose a current or future threat to public health. This updated 2013 Report has the same objectives. It is important to acknowledge that medicines are of course not the only intervention to prevent, treat and diagnose diseases. In this report, vaccines and diagnostics have therefore also been identified as potential priority areas.

The objectives of this report must be set against a backdrop of the key demographic changes that are transforming the global disease burden (Chapter 5). Low- and middle-income countries are currently facing a shift in their disease burden from one that is dominated by communicable diseases towards one dominated by chronic noncommunicable diseases (NCDs). This change has profound implications for health care systems and the development of innovative medicines. These changing disease burdens are entirely predictable. The key drivers are both demographic and epidemiological and include factors such as the ageing population and changes in risk factors such as tobacco and alcohol use as well as obesity which are leading to the increasing prevalence of chronic NCDs. As a result, health systems in many low- and middle-income countries will face a double burden of disease, as NCDs add to the existing burden of communicable diseases and reproductive health problems addressed in the Millennium Development Goals 4, 5 and 6.

While the first part of the report, Chapters 1 to 6, identifies high-burden diseases and substantial risk factors for which pharmaceutical gaps exist, Chapter 7 takes a more holistic approach and looks at common themes around children, women, the elderly and the new concept of stratified medicine. Chapter 8 builds on work done in the 2004 Report to identify incentive systems for pharmaceutical innovation in Europe, that increase efficiency and equity and involve patients and citizens in key decisions that affect them. The chapter suggests multiple approaches for addressing identified pharmaceutical gaps, including through proposed incentives for the pharmaceutical industry.
9.2 Methods used in the updated 2013 Report

The methods used in the updated 2013 Report are similar, but not identical, to those used in the 2004 Priority Medicines Report (see Chapter 4 and the related Background Paper). Several key criteria were used to define a preliminary list of diseases which would be reviewed in depth. To this end the WHO Global Burden of Disease dataset was used to determine the highest disease burdens in Europe and the world, with the explicit inclusion of critical risk factors (tobacco and alcohol use and obesity). In addition, the concept of social solidarity (rare diseases, neglected tropical diseases), and public health projections (pandemic influenza and increasing antimicrobial resistance (AMR)) were used as additional criteria, as in the 2004 Report. However, in contrast to the 2004 Report, the pharmaceutical gaps were not investigated via a Cochrane analysis prior to writing full reviews. Such investigations were included as part of the full in-depth reviews (Chapter 6.1- 6.24) and are presented in the background papers. Authors of the reviews identified research topics which would be the most beneficial from a public health point of view.

Data sources were expanded from the original WHO 2004 Global Burden of Disease dataset to include the WHO projections for both Disability Adjusted Life Years (DALYs) and mortality for 2008 as well as data from the 2010 Global Burden of Disease Study (GBD 2010 Study) as published in The Lancet in December 2012. However, the GBD 2010 Study used a different methodology and different geographical regions, making it challenging to compare the burden of disease results between the WHO projections and the GBD 2010 Study. All previously reviewed diseases from the 2004 Report were again included in the final list of detailed reviews in the 2013 Report. In addition, some new topics that emerged as relevant in the top 20 diseases in the GBD 2010 study were included. This resulted in the addition of six new diseases and risk factors due to their high disease burden: obesity, diarrhoeal diseases, hearing loss, pneumonia, neonatal conditions and low back pain.

Under cross-cutting themes (Chapter 7), a new section is included on stratified medicine because of its potential impact on clinical practice over the next decade. In the chapter on incentive systems for innovation (Chapter 8), new sections have been added on the use of real-world data through the availability of electronic health records (EHR) to support innovation and on the role of patients and citizens in priority setting for pharmaceutical innovation.

9.3 Priority medicines and pharmaceutical gaps

“Priority medicines” as defined in this report are medicines which are needed to meet the future priority health care needs of the population. They are needed because a treatment gap exists for a number of high-burden diseases and conditions. Different types of treatment gaps include:
9. Conclusions and recommendations

**Gap 1:** Treatment(s) exist but will soon become ineffective;

**Gap 2:** Treatment(s) exist but the pharmaceutical delivery mechanism or formulation is not appropriate for the target population;

**Gap 3:** Treatment does not exist OR is not sufficiently effective.

The three categories are non-exclusive. For example, malaria could be placed in Gap 1 (medicines will become ineffective due to AMR) or Gap 3 (no medicines or vaccine exists) as no malaria vaccine is available. Similarly, HIV might be placed in Gap 2 (treatment is available but there is a need for paediatric formulations) or Gap 1 (the current treatment might become ineffective) or Gap 3 (no vaccine exists).

While the focus of this report is on pharmaceuticals needed to fill treatment gaps, the importance of prevention cannot be overemphasized. For many conditions prevention is of paramount importance and remains underutilized for conditions and risk factors such as chronic obstructive pulmonary disease (COPD), liver cirrhosis, type 2 diabetes, tobacco use, alcohol consumption and obesity. A fourth category has therefore been created (Gap 4) to address the problem of key risk factors for disease (obesity, tobacco use, alcohol use).

A brief summary and recommendations are provided below for each of the diseases, conditions and risk factors identified. More information on these conditions can be found in the individual sections of Chapter 6 and in the background papers.

**9.4 Gap 1: Treatment(s) will soon become ineffective**

*Antibacterial resistance*

Antimicrobial resistance remains a serious threat to global health, with an increase in the spread of new highly-resistant organisms, including many Gram-negative bacteria and those causing tuberculosis (TB) and malaria. Some progress has been made since 2004 with increased funding from the Innovative Medicines Initiative (IMI) for research into AMR. Continued surveillance is needed both in Europe and worldwide as well as close cooperation between countries in order to combat the threat of AMR. There also remains a need for new and rapid diagnostics, for new business and R&D models, and for alternatives to the use of antibacterials, such as substances to modify host/pathogen interactions or vaccination for primary prevention of infection. As stressed by the European Commission and public health authorities, vaccination can and should play a key complementary role in anti-microbial resistance programmes.

*Pandemic influenza*

Since 2004, an influenza pandemic has occurred, stimulating the development and mass production of new types of vaccines. In the current inter-pandemic period, various gaps exist in therapy and access to vaccines. Among these challenges are: the low uptake of inter-pandemic seasonal immunization, which limits production
capacity and restricts the world’s surge capacity in times of a pandemic; rapidly mutating viruses that require new vaccines (including adjuvanted vaccines); and the need for more antiviral compounds. More sensitive rapid diagnostic tests for influenza are needed in order to detect and distinguish between influenza virus subtypes. New antiviral agents are needed with broad reactivity against all virus strains and sub-types.

9.5 Gap 2: Treatments exist but the delivery mechanism or formulation needs to be more appropriate to patient use

Cardiovascular disease

Despite ongoing research, no new ‘breakthrough’ medication has been developed with the potential to improve on the existing generally effective treatment used by patients with established cardiovascular disease (CVD). The focus here is therefore on better use of existing medicines, particularly in high-risk individuals who have already had a heart attack or stroke. This includes the potential use of a “polypill” of four effective generic medicines for the secondary prevention of ischaemic heart disease (IHD) as already recommended for study in the 2004 Report. This combination product is now available but needs to be evaluated with a large-scale trial to demonstrate its impact on mortality rates and on prevention of repeat heart attacks or strokes in survivors of first events. There is also a need to identify barriers to improving the prevention and treatment of CVDs and strategies to overcome these barriers.

HIV/AIDS

HIV/AIDS continues to be one of the deadliest epidemics of our time. There has been a reduction in the rate of new infections worldwide, in part due to increased roll-out of treatment with antiretrovirals. However, there is still a need for approved formulations for children as well as paediatric diagnostic tests. Not all the viral targets have been explored and new modalities of treatment are still possible. Funding and research for the development of an HIV vaccine should be maintained.

Cancer

Since 2004, there have been a number of major therapeutic breakthroughs resulting from a better understanding of the biology of cancer and the identification of tumour-specific biomarkers. However, targeted therapies are needed that improve survival, together with a concerted effort to address cancer in children. In addition, the major disparities in cancer care and epidemiology between high-income and low- and middle-income countries should be addressed. The affordability of cancer therapeutics is also of great concern, but this is difficult to address without changes in the way health care systems are organized.
9. Conclusions and recommendations

**Depression**

Treatment gaps for depression persist. Too many antidepressants have serious adverse effects and for that reason about half of the patients discontinue treatment within the first six months. Research is needed to better understand the link between genetic factors and the efficacy and safety of treatment. Safer treatment alternatives for adolescents are required and many health system barriers to treatment remain to be addressed. Work is also needed on the development of biomarkers and new delivery methods.

**Diabetes**

Diabetes and diabetes-related illnesses place an enormous burden on the health care systems of most countries throughout the world. There is an alarming increase in the incidence of type 1 diabetes (currently incurable) and an increase in the prevalence of type 2 diabetes, especially in low- and middle-income countries. It is estimated that about half of all cases are undiagnosed. There is a continuing need for the development of a heat-stable version of insulin (mainly for use in developing countries), and new treatments are needed that mimic the bodily response to glucose. An effective solution is needed to counter the progressive loss of beta-cells in those with type 2 diabetes, which accounts for the vast majority of people with diabetes. In addition, a pharmacological strategy is required to reduce the problems associated with polypharmacy for patients with several risk factors for diabetes, such as the development of single drugs or fixed-dose combinations with multiple targets that affect several risk factors such as dyslipidemia, hypertension and obesity.

**Pneumonia, diarrhoeal diseases and neonatal diseases and conditions**

Effective treatments for bacterial pneumonia exist but there is a need for better and more rapid diagnostic tests with the ability to distinguish between viral and bacterial pneumonia, and for new formulations of antibiotics for use in infants and newborns. Further R&D is vital in order to bring promising vaccine candidates for pneumonia and diarrhoea on to the market. Neonatal conditions account for a high proportion of the global burden of disease. Research is needed to develop new therapies to address the problem of preterm births, neonatal sepsis and birth asphyxia. With regard to preterm birth there is a need for the development of tocolytics with fewer side-effects in mothers and newborns and for clearly labeled, pre-packaged or pre-filled delivery systems for antenatal corticosteroid products. For neonatal sepsis there is a need for the development of shorter course antibiotics, oral antibiotics, and antibiotics with fewer side-effects for newborns; rapid diagnostic tools for neonatal conditions in order to avoid the inappropriate use of antibiotics (thereby lowering the risk of AMR); and appropriate smaller dosage forms for newborns. To prevent birth asphyxia, research efforts should include the development of effective and lower-cost synthetic surfactants and a more stable oral surfactant.
Malaria

Since 2004, there has been a substantial decline in the incidence of malaria combined with better access to effective medicines (artemisinin combination therapy) and insecticide-impregnated bednets. This is largely due to an unprecedented financial commitment by global donors over the past decade. In addition, the widespread and reliable use of rapid diagnostic tests has helped ensure that malaria, and not other conditions, are treated with antimalarials. Although there are several promising antimalarial therapeutic candidates in the development pipeline, resistance will remain a threat until an effective vaccine is available to prevent the disease. Continued support is needed for research on the development of vaccines, new medicines and rapid diagnostic tests for use in low-prevalence settings.

Tuberculosis

Tuberculosis (TB) remains mainly a disease of poverty with a high burden in low- and middle-income countries and in countries with high HIV prevalence. Today, new funders are investing in R&D for TB. Rapid diagnostic tests are now available, but there is a need to improve existing diagnostic tests for use at various levels in the health care system, in diverse patient groups and in high-burden settings. Although the TB medicine pipeline is growing, more effective and safer treatments are still needed due to the development of multi-drug resistance. The development of fixed-dose combinations of the new regimens and more suitable formulations for children would be a major advance. Meanwhile, research is ongoing to find a new, more effective vaccine.

Neglected tropical diseases

Of the 1556 new drugs approved in Europe and the United States between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and TB. Although there is more commitment now and a promising pipeline of products, more effective diagnostics and treatments are still needed, particularly for leishmaniasis, trypanosomiasis and dengue. Some medicines are inappropriate for tropical environments and need to be re-formulated. Meanwhile specific formulations for children and neonates are still needed for many diseases.

Postpartum haemorrhage and maternal mortality

Postpartum haemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. As a result of the 2004 Report, successful research was undertaken to understand the thermal stability of oxytocin. However these findings need to be applied to help accelerate the development of heat-stable oxytocin in a single-dose system which can be used by midwives to actively manage the third stage of delivery.
9.6 Gap 3: Treatment does not yet exist or is insufficiently effective

As in 2004, stroke, osteoarthritis, COPD, and Alzheimer disease and other dementias were identified as high-burden diseases with very limited therapeutic options. In addition, hearing loss and lower back pain are now added to the list. Some progress has occurred in identifying biomarkers of disease onset or progression, for instance in Alzheimer disease and osteoarthritis, but these biomarkers lack the sensitivity required for diagnosis and clinical trials. For these and other diseases, the development of diagnostic measures (including the use of biomarkers) and new treatments remain the priority.

**Acute stroke**

The current treatment of acute stroke is unsatisfactory, and investment is needed for basic and clinical research to develop new treatments. Most agents are not sufficiently effective and some are associated with an increased risk of adverse events. Progress in the fields of neuroprotection and stem cell research are badly needed. Some progress has occurred in establishing biomarkers to identify or measure progress, but none are fully validated for use in drug development or to evaluate clinical impact. The development of diagnostic measures, including the use of biomarkers, remains the first priority. Barriers to effective secondary prevention need to be identified.

**Osteoarthritis**

Osteoarthritis is the single most common cause of disability in older adults. There are currently no medicines that can cure, reverse, or even halt the progression of the disease. The available diagnostic tools have low sensitivity and specificity. The lack of valid biomarkers limits pharmaceutical development and clinical monitoring. Some progress has occurred in identifying biomarkers that could be used to identify or measure progression of the disease, but none are fully validated for use in drug development or to evaluate clinical impact. The first priority is therefore the development of diagnostic measures, including the use of biomarkers.

**Alzheimer disease and other dementias**

With the ageing of the population both in Europe and worldwide, managing Alzheimer disease and other dementias is becoming a major concern as governments are poorly prepared to face the magnitude of the situation unless effective treatment becomes available. In 2008, the WHO launched the Mental Health Gap Action programme which included dementia as a priority condition. This was then followed by a major report in 2012. There are currently no specific tests that can positively confirm a diagnosis of Alzheimer disease, and no treatment can delay its onset or affect the course of the illness. Some progress has occurred in identifying biomarkers that could measure progress but none are fully validated for use in drug development or for evaluating clinical impact. The development of diagnostic measures, including the
use of biomarkers, therefore remains the priority. These markers are essential as they can provide new pathways for research and pave the way towards better understanding of the onset of the disease. The development of existing bio-banks including tissues, blood, urine and cerebrospinal fluid from patients and healthy volunteers should help identify such markers.

**Chronic obstructive pulmonary disease**

The burden of COPD is increasing, but there is a general lack of public awareness of the disease. For this condition prevention through tobacco use cessation is critical. Currently there is no effective cure for COPD and medicines are needed to halt or slow down the progression of the disease, not just to control the symptoms. An effective diagnostic test and effective COPD anti-inflammatory treatments are required. New information on the inflammatory progress and surrogate biomarkers is also needed.

**Hearing loss**

At present, the use of cochlear implants and hearing aids is the only way to partly recover hearing and communication skills. However, these devices can be very expensive and are therefore not always affordable. A cure for hearing loss, which is associated with ageing, would be a tremendous advance in public health. More progress is therefore needed in pharmaceutical research to treat or prevent hearing loss. Primary prevention of hearing loss in low- and middle-income countries through immunization against measles, rubella and *Haemophilus influenzae* type b (Hib) has been successful. There is a need to assess the potential health benefits and economic impact of vaccines targeting other pathogens that impair hearing. Consortia of European research and industrial partners could contribute to strengthening the EU’s leadership on research into the pharmacological prevention and treatment of this frequent disorder, which has received little attention so far.

**Low back pain**

Low back pain affects people of all ages, from children to the elderly, and is a common reason for medical consultations. As the world population ages, low back pain will increase substantially. At present there are no pharmaceutical interventions that can cure back pain, and only palliative care is possible. There is also a need for validated biomarkers for low back pain. Meanwhile, three-dimensional imaging should be further investigated to help to diagnose and monitor progression and design disc prostheses.

**Rare (including orphan) diseases**

In the EU, a disease is considered “rare” when the number of people affected is less than 5 per 10 000. The causes of many rare diseases are unknown and this can result in a missed or delayed diagnosis. There has been considerable progress since 2004 in developing disease-specific products but often at high prices. Gaps in clinical
evaluation call for an internationally recognized rare disease classification system which would help in generating reliable epidemiological data. A public database should be created, underlying an infrastructure of earlier epidemiological surveillance. There is a need to develop easier diagnostics, biomarkers and site-specific delivery systems. Continued support for networks remains important for such infrequent cases.

9.7 Gap 4: Global risk factors with no or insufficient pharmaceutical treatment

This report also addresses the leading risk factors for disease that might be amenable to pharmaceutical solution(s). Such solution(s), if found and made available, should be used in concert with other preventative interventions related to personal and societal factors.

**Tobacco use cessation**

Tobacco use continues to be the leading cause of preventable deaths, despite aggressive national educational campaigns and fiscal policies. Smoking cessation products are rarely reimbursed by health or insurance schemes. More effective safe medicines are needed to achieve long-term abstinence. Research is also needed on the cost-effectiveness of pharmacotherapy for smoking cessation in low- and middle-income countries to inform decision makers about the need for the development of lower-cost therapeutic options for their countries. Some new treatment options are available and various smoking antagonists are in the pipeline. However, it is necessary to determine the safety, efficacy and effectiveness of existing and new therapeutic modalities for specific patient groups (including adolescents and pregnant women), as well as a better definition of the criteria for using some of the therapeutic modalities in combination.

**Obesity**

Only very limited pharmacotherapeutic treatment options exist for obesity. Only one product is available in most European countries (orlistat) and no current pharmacotherapy can produce clinically significant long-term weight loss (at least 5% to 10% weight loss) in a large proportion of morbidly obese patients. Safety concerns (mainly due to central nervous system and cardiovascular effects) have resulted in the decision by medicines regulatory authorities not to approve or even withdraw marketing approval. Biomarkers are needed to identify those individuals most likely to benefit from available interventions and long-term studies are needed to prove safety. New pharmacotherapeutic options are urgently needed to treat those already affected by morbid obesity. More research is needed on adherence, on regaining body weight after discontinuation of pharmacotherapy, and on the cost-effectiveness of different therapies.
**Alcohol-related diseases**

The EC has funded research on alcohol use disorders and alcohol-related diseases and some new medicines have shown promise in conjunction with behavioural therapy. There is poor understanding of liver pathogenesis and the treatment for liver cirrhosis has low effectiveness. The outlook is poor in the short- and medium-term for development of new therapies for diseases and conditions related to alcohol abuse. The major need is for translational research to convert basic science advances into products that can be used in clinical trials.

**9.8 Cross-cutting themes**

The following cross-cutting themes apply to all diseases and therapeutic approaches. The two major themes in Chapter 7 include the particular needs of special groups (children, women and the elderly), and the concept of stratified medicine which enables targeting of treatment to sub-populations more likely to respond or less likely to be harmed.

*Summary of key points and recommendations for cross-cutting themes*

Despite the adoption of new regulations and other initiatives by regulatory authorities, which have led to some progress, children and the elderly are still underrepresented in clinical trials. Important information is often lacking on dosing, effectiveness and safety for children and the elderly and many medicines used in these populations are therefore prescribed “off-label”. Similarly, there is a shortage of gender-specific analysis and data on the use of medicines during pregnancy. However, stronger regulations are not considered as the most appropriate way forward. New approaches, such as better use of existing electronic health records (EHR) (see also Chapter 8.4), may be more valuable in obtaining the much needed data on safety and effectiveness of medicines in children, (pregnant) women and the elderly. It is also important to translate this age- or gender-specific information into practical recommendations. In addition, existing data could assist in stratified medicine and in identifying populations at highest risk for adverse events (safer use of existing medicines) and treatment responders (targeted use of expensive medicines), thereby leading to more effective pharmaceutical care.

Children and the elderly have several similar difficulties in taking their medication. Adapted, age-appropriate children’s medicines have been developed over the past decade, with especially innovative oral solid dosage forms. Continued R&D investments are required for new routes of administration, safer excipients, responding to patient preferences and patient-related outcomes such as adherence, efficacy and side-effects. For the elderly, alignment is needed with the development of formulations for children, taking into account the differences between the two populations. Moreover, tools to assess and improve medication self-management among elderly people living independently should be further developed and evaluated.
Polypharmacy is very common in the elderly. Although interventions to address polypharmacy can lead to more appropriate prescribing and fewer medication-related problems, it is unclear how this improved practice can be translated into clinical outcomes such as reduced hospital admissions and lower mortality rates. More research in this area is needed to inform policies and practices. The supporting role of EHR needs to be improved, and the added value of fast and extensive data sharing with the aid of computerized systems needs to be established. Sharing of information and communication between health care professionals is also vital for integrated and continuous care, particularly in the elderly patient living with several coexisting diseases. Approaches that support advanced integration of care need further investment.

Clinical implementation of stratified medicine with personalized diagnosis and treatment has been limited until today, but holds the promise of better use of existing medicines in all settings, and of the identification and development of drug targets, new medicines and diagnostic tools. Limitations currently hampering the attainment of the full potential of stratified medicine can be addressed by the following seven strategies: (1) stimulating pharmacogenomic approaches to existing medicines, (2) stimulating the use of multi-dimensional analyses (integration of biomarkers and clinical parameters), (3) establishment of a European research network and a European catalogue of pharmacogenomic datasets with a harmonization programme, (4) adaptation of regulatory guidelines and reimbursement procedures, (5) the development of a framework to assess comparative (cost-)effectiveness, (6) development of harmonized training and education programmes for health care professionals and the public, and (7) research into the ethical, legal, economic and social implications of stratified medicine.

### 9.9 Incentive systems for pharmaceutical innovation

Pharmaceutical innovation is the key approach to address the gaps described above, and some general barriers to innovation need to be addressed. A pharmaceutical gap can occur when market forces fail to meet public health needs. By identifying incentives for and barriers to pharmaceutical innovation, action can be taken to facilitate the development of new medicines to fill pharmaceutical gaps. Although substantial progress has been seen in some therapeutic areas (e.g. cancer, multiple sclerosis, rheumatoid arthritis), there is still growing concern about the inefficiency of the drug discovery and development process for new medicines for unmet medical needs. Whether this decline in R&D productivity is due to research depletion, too strict regulatory hurdles, or the current pharmaceutical business model remains unanswered.
Public-Private Partnerships and Innovation

Public-private partnerships (PPPs) were mentioned in the 2004 Report as a promising solution for filling the pharmaceutical gap. Since 2004, there has been great progress in the development of PPPs, in particular the Product Development Partnerships (PDPs). Partnerships focusing on TB, malaria and neglected tropical diseases as well as diagnostics for neglected tropical diseases have had considerable success. For example, the Top Institute (TI) Pharma in the Netherlands and the Innovative Medicines Initiative (IMI) have developed into effective partnerships focusing on precompetitive research. All such partnerships face a challenge in that funding time-lines are often short while drug or diagnostics development takes a long time. Reconciling this tension with long-term funding commitments will be necessary for these partnerships to fulfil their great potential. There is a need to identify the most successful models for PPP collaboration. Knowledge about what are the most useful indicators (structural, process, output or outcome) of successful partnerships would be beneficial for all those involved. Another area for research is stakeholder participation (including patients and citizens) in PPPs and their involvement in the decision-making process. Chapter 8.5 contains a number of research recommendations that are also relevant for PPPs.

Regulation and innovation

Regulation plays an essential role in balancing societal expectations of new medicines addressing unmet medical needs and ensuring a favourable benefit-risk profile for these medicines. The 2004 Report called for a re-examination of the regulatory process and for a critical analysis of the evidence base for regulatory practices using modern methodologies. Since then, networks for analysis and information sharing have been initiated across Europe and numerous studies have been undertaken on different aspects of the regulatory system. However, research methodologies are still under development and should be further refined. Other examples of progress in this area are better communication between stakeholders (regulatory dialogue) and strengthening of the role of post-marketing surveillance.

Despite these developments, challenges remain. Additional research is needed on promising instruments to optimize regulatory requirements for initial marketing approval (e.g. the use of surrogate outcome measures and an adaptive study design) and on quantitative instruments supporting more standardization of benefit-risk assessment. In line with the adaptive licensing proposals, more studies are needed to reduce uncertainty around effectiveness and safety, while measuring and comparing the effects of medicines in real-life settings. Improving this kind of learning could help to achieve an adequate level of safety knowledge while requiring less data to be collected pre-approval.

Measuring the (cost-)effectiveness of regulatory policies is an important challenge. In order to evaluate and improve existing regulations and to base new incentives on best practices, impact measures should be defined explicitly in terms of quantitative and qualitative performance indicators, and monitored in carefully designed studies.
Collaboration and dialogue between all actors, including the involvement of patients and citizens in the regulatory system, should be supported at multiple levels (see Chapter 8.5 for priorities on patient involvement in decision making).

Close collaboration is also needed between regulatory agencies and academia to test and explore new methods for drug development and regulatory decision making. The new field of regulatory science, studying the performance of the system as a whole, would benefit from investments in sharing and analysing existing and future regulatory datasets.

**Pricing, reimbursement and innovation**

Many European countries share the implicit or explicit health policy objectives of sustainability, equity and quality of care, but the way in which these are handled can differ substantially between countries. Pricing and reimbursement policies used in the EU include external price referencing, internal reference pricing, decision-making based on Health Technology Assessment (HTA) and economic evaluations, value-based pricing, caps and co-payments, taxes, price-volume agreements, fixed margins in distribution channels and tendering. The 2004 Priority Medicines Report highlighted differential pricing as a key policy for the future and also put a strong emphasis on pharmacoeconomics as a tool to value new medicines. Since then, more European countries have incorporated HTA and economic evaluations in their reimbursement – and sometimes pricing-policies. In most of Europe, however, external price referencing remains the predominant pricing method. An alternative to external price referencing is value-based pricing, in which the price of a new medicine is determined by the (added) value it generates. These policies are now (being) implemented in a few countries.

The 2013 Report identifies three different broader topics for future research. Firstly, research priorities that focus on the broader environment of pricing and reimbursement policies: studying the meaning of innovation for pricing and reimbursement authorities, the impact of the financial crisis, evaluation of new regulations and the link between pricing and availability at a global level.

Secondly, a set of research priorities focus on some of the main methods used for pricing and reimbursement policies: the effects of external price referencing (both beneficial and adverse effects), the experience with the implementation of value-based pricing policies, differential pricing mechanisms and policies (especially official list prices and informal discounts and rebates), volume control (generic policies and practices, managed-entry schemes), models for small volumes (medicines targeting rare diseases and stratified medicines), and patient involvement (see Chapter 8.5). Thirdly, for all these studies, cross-national learning, co-development of methodology and exchange of information and experiences are critical. To achieve these objectives, it is therefore essential to build an appropriate research infrastructure.
Use of real-world data to support innovation

Data obtained from health systems is critical to support innovation as this information plays a vital role in closing the gap between clinical research and clinical practice, thereby improving the whole medicine development chain including regulation, pricing, reimbursement and treatment decisions. Electronic health records (EHR) are currently the most important source of information to capture the real-world setting, and should be used to assess the effectiveness (real-world effects) and safety of medicines, especially in populations that are not sufficiently included in clinical trials. The use of EHR databases for research into stratified medicine is a more recent development. Other important new uses have also been identified, including: use for better understanding of diseases; identifying adherence failure; predicting risk; and comparing effectiveness. Moreover, policy initiatives such as adaptive licensing, value-based pricing, policy evaluations and priority setting are critically dependent on optimal use of EHR data.

Current challenges are the fragmentation of the resources available in Europe and the limited availability of good quality data, often limited to a specific disease area or geographic region. Many important research questions call for larger databases, highlighting the need for performing studies across different EHR systems and countries and finding ways to integrate the results. To foster pharmaceutical innovation, a European research network should be established for comparative effectiveness and health policy evaluations using EHR data. New statistical models are needed for the systematic measurement of EHR data quality, new methods are needed to predict long-term risks through the use of EHR databases, and a European EHR database should be established to make explicit the uncertainties in routinely used interventions.

Patient and citizen involvement in innovation

The final section in Chapter 8 addresses patient and citizen participation in priority setting for pharmaceutical innovation, which was only briefly mentioned in the 2004 Report. Since then, patient involvement has received substantial attention from patient organizations, policy makers, governments and researchers. The number and variety of initiatives, models and frameworks that have been developed reflect the broad acknowledgement of the value and importance of patient and citizen involvement. However, these initiatives have not yet resulted in a widely accepted model or a framework for meaningful involvement. Such a framework is needed to ground patient and citizen involvement in an evidence base and to optimize its practice.

Although a framework is essential, it will remain weak and indecisive in the absence of people and organizations willing and able to realize the potential of patient and citizen involvement. Hence, capacity building is needed to realize meaningful involvement. In addition, other research efforts are needed to establish best practices for patient and citizen involvement (e.g. identification of barriers to meaningful involvement, design and evaluation of measures to overcome these barriers, and the development of
strategies to ensure the primacy of the interests of patients and society). Another important research recommendation is to ensure that effective assessments of initiatives to involve patients and citizens are undertaken and published. Critical scrutiny of initiatives would include cost-benefit assessments in addition to regular effect measurements.

9.10 The role of the European Commission in supporting research for health

It should be recognized that much of the progress that has occurred since the 2004 Report has been as a result of activities undertaken by the European Commission, particularly DG Research. These activities are well documented on the Community Research and Development Information Service CORDIS (http://cordis.europa.eu/home_en.html). However, while CORDIS reports call for research and awards, when awards are made, information on project outputs and outcomes may be delayed and the project website is often shut down when project funding is completed. This information asymmetry in CORDIS is similar to that of the United States National Institutes of Health (NIH) which has established an Office of Portfolio Analysis to address this and related issues. It is recommended that the EC establishes an open archive for the web pages of these projects, which should be uploaded at the time of project completion.

9.11 Final comments

This 2013 Report Priority Medicines for Europe and the World identifies key areas of priority research for pharmaceutical innovation to meet public health needs. In providing an update to the 2004 Report, the present report has been able to highlight areas where important progress has been made and those where additional investment is needed.

To improve the health of the people of Europe and the world will require innovation to develop new and better medicines, vaccines and diagnostics that can be used efficiently and equitably in existing health systems with sustainable financing. The European Union has done much to ensure that this vision continues to be fulfilled.