# Update on 2004 Background Paper, BP 2 Background

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Background to Priority Medicines Project: Pharmaceutical Innovation and its Policy Environment

Biomedical technology companies seek to conduct research and commercialize products in a stable, predictable operating environment that encourages and rewards innovation. These companies are accountable to the shareholders and customers they serve. The pressures being placed on pharmaceutical companies, from within and without, can negatively impact innovation. The resources required for drug development have risen markedly in the past 30 years, so that these costs may threaten to make the development of new drugs increasingly unaffordable for both companies and consumers. From a business viewpoint, this ever-increasing cost of drug development is an incentive for companies to invest in products likely to provide the highest rate of return on research and development (R&D) investment. This incentive is often realized by developing drugs against proven targets using approaches that have already been clinically and financially successful, although some companies attempt the difficult task of having projects with higher success rate but a lower potential return as well as projects with a higher risk but potentially higher reward.

Notwithstanding, pharmaceutical research has a high failure rate. Of every 5000 projects only one completes the drug development process and, of those that do, only one in five actually returns its R&D investment. Regulators have progressively increased the requirements for product authorization in a quest to promote safety and efficacy. Reimbursement authorities have often been more interested in controlling drug costs rather than considering total healthcare benefit. Providing appropriate incentives for developing products targeted for important public health needs, less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging.

Key drivers of pharmaceutical innovation from both supply and demand perspectives can include:

- a high level of public interest in health care issues
- strong public support for increasing national, public sector research funds
- increasing private investment in medical R&D, although private sector interest fluctuates depending on other business opportunities
- size of the market and expected return on investment
- changing demographics such as an ever-aging population which alters research priorities to other diseases (e.g. Alzheimer disease, diabetes, chronic diseases)
- public expectations about who performs high quality science
1 What is Pharmaceutical “Innovation”? 

There is a rich and varied theoretical and empirical literature on innovation generally and on pharmaceutical innovation specifically.3,4,5,6 The definition and even the existence of “pharmaceutical innovation” varies according to the viewpoint of the definer along the pharmaceutical value chain. Pharmaceutical innovation ranges from breakthrough treatments for life threatening diseases to minor modifications of drugs that have been on the market for some time. From the point of view of regulatory agencies and their largest “customer”, the pharmaceutical industry, it is worth noting that the United States Food and Drug Administration (FDA) classifies innovation in two dimensions: by chemical type and therapeutic potential. (See updated Background Chapter 3). New products, can qualify for a priority regulatory review by demonstrating one or more of: evidence of increased effectiveness; reduced side effects and interactions; enhanced compliance; or use in a new subpopulation. From a public health viewpoint, these latter four factors are important. The real value of any medicine emerges most clearly once it has been introduced into medical practice and it supports our view that the answer to "what is pharmaceutical innovation?" depends on who is asking the question.

2 Trends in Pharmaceutical Innovation

Although the data can be subject to different interpretations, certain students of innovation.7,8 have suggested that innovation in the pharmaceutical industry occurs in waves of activity, postulating the existence of several successive "generations" of medical (and other) technologies over the past two hundred years.9

Very briefly (see reference 6 for more details), first generation innovations (1820-1880) were a consequence of the "Chemical Revolution" introduced by Antoine Lavoisier and the French School of Chemistry at the end of the 18th century. The development of chemical extraction and experimental methods allowed isolation and purification of "active principles" of medicinal plants (e.g., morphine, quinine, curare, belladonna) with known medicinal properties. Such methods also allowed for the synthesis or isolation from plants or coal tar of simple organic chemicals with medicinal properties (e.g., ether as an anaesthetic, chloroform as a hypnotic, carbolic acid as an antiseptic, salicylic acid as an antipyretic).

Second generation innovation (1880-1930) was driven in large part by scientific and industrial responses to social conditions in the expanding cities of the Industrial Revolution. Overcrowding, poverty, malnutrition, lack of running water and public sanitation facilities caused the spread of infectious disease, such as smallpox, typhoid fever, tuberculosis, cholera and diphtheria. What developed during this time period were public medical research laboratories for sera and vaccines (e.g., Pasteur Institute, Lister Institute, Rockefeller Institute, Berlin Institute for Contagious Diseases, Kitasato Institute and German, French and Swiss dyestuffs companies (Bayer and Hoechst, Ciba, Sandoz, Hoffman LaRoche, Poulenc Freres and Etablissements du Rhone)) with increasing expertise in organic chemistry. This led to establishment of the modern pharmaceutical industry.
The third generation (1930-1960) included innovations in organic and natural products chemistry leading to the isolation and synthesis of vitamins, corticosteroids, sex hormones and antibiotics. Laboratory analytical methods for composition and structure determination requiring very small samples (e.g., infrared, ultra-violet and nuclear magnetic resonance spectroscopy, X-ray crystallography and paper chromatography) were developed as well as various in vitro and in vivo screening assays for evaluation biological and medicinal properties of compounds. A major development during the third generation, together with research intensity, was the adoption of intensive marketing methods aimed at physicians, hospitals and drugstores.

Innovations of the fourth generation (1960- about 1980) resulted from a marked shift in the scientific basis of the industry from chemistry and pharmacology to the life sciences. The most important drugs of the 1960s and beyond were used for the treatment of chronic diseases such as cardiovascular, central nervous system and cancers. Their development necessitated the understanding of the mechanisms of biological and physiological processes at the molecular and cellular level. Due to the proliferation of drugs, the increasing competition among companies for the same patient populations, and of the thalidomide incident in 1961, governments imposed strict regulatory measures for the conduct of clinical trials, and the approval of new medicines, which required the provision on the part of innovating companies of substantial evidence for the effectiveness and efficacy of candidate drugs.

The latest "generation" (since 1980) is based on advances in discovery and application of biotechnology (recombinant DNA and monoclonal antibody methods) in the production of physiological proteins used in therapy or diagnosis of many diseases. See references 3, 6, 9 for further details.

Figure 2.1 (taken directly as Figure 8 from reference 6) is an early but telling description of innovation in the pharmaceutical industry. The successive "waves" of innovation are clear but we note the precipitous downward trend up until 2000. This is a powerful reminder of the changing nature of the pharmaceutical industry and that, in the face of ever increasing R&D costs, the output of innovative pharmaceuticals from the "pipeline" is sluggish. To be sure, the number of innovative medicines approved by the FDA is occurring at least a decade after initial investment in R&D. This emphasizes the need to understand how the present R&D spending is being translated into new medicines going forward.

We further note that even FDA new molecular entity submissions for marketing approvals have been approximately the same over the past decades (see Section 2.1 below). We note in this regard that, notwithstanding, the total number of drugs in active development (i.e., all drugs in the pharmaceutical companies' pipeline, pre-clinical and clinical) apparently has not. The important point in this regard is that while the number of projects in phases I and II is constantly increasing, the number of projects in phase III has stalled. There is a need to more efficiently translate these early stage projects into approved medicines.
2.1 Current challenges to biomedical innovation

We reiterate that, although investment in pharmaceutical R&D in Europe and the United States has increased since the Priority Medicines Project report in 2004, there has not been a corresponding increase in the output in terms of new drugs being approved. Thus in both Europe and the United States (still the major global sources of innovative medical products), it would appear that therapeutic innovation has become more challenging. The cost of developing a new drug has increased, as have total R&D expenditures,\(^{12}\) while the rate of introduction of new molecular entities (NMEs) has remained about the same \(^{13}\) and attrition rates have risen sharply, especially in late-phase clinical trials.\(^ {14}\) Figure 2.2 (adapted from reference 12) summarizes some of the recent information on the apparent slowdown in pharmaceutical innovation. In essence, panels c and d suggest that the current pharmaceutical innovation model needs to be altered in order for there to be significant increases in output of new molecules. Put another way, the present rate of discovery of NMEs simply reflects the capacity of the pharmaceutical industry.

The reasons for this are complex. In short, however, the ability of the major pharmaceutical industries to innovate is under growing pressure from losses of revenue owing to patent expirations, increasingly cost-constrained healthcare systems and more demanding regulatory requirements.\(^ {15}\)

From a public health viewpoint, a new use for an ‘old medicine’ is clearly an innovation. In the case of studies of metformin in cancer, it would appear that a loss of revenue and lack of funding incentives are barriers. Metformin, which Bristol-Myers Squibb Co. sold in the United States as Glucophage\(^ {®}\), lost patent protection years ago, meaning that manufacturers no longer reap significant profits from its sale. See Box 2.1 (copied as fair use from Bloomberg.com and ip-health (29 September 2012).

However, more recent analysis shows that in 2011, the United States Federal Drug Administration (FDA) approved 30 NMEs, excluding new biologicals. The 30 NMEs approved in 2011 represent the second highest total in the period 2002 to 2011, after the 32 NMEs approved in 2004 (see Figure 2.3). In 2012 the FDA approved 39 NMEs.
**Figure 2.2: Decline in pharmaceutical innovation**


a | The cumulative number of new molecular entities (NMEs) originating from the three most productive companies over the period studied: Merck, Lilly and Roche. b | The cumulative number of NMEs from selected companies that have been heavily involved in mergers and acquisitions, with Lilly included for comparison. c | The NME output of the industry closely tracks the expected value on the basis of the statistical analysis (ref. 12) suggesting that output is not depressed at present, but simply reflects the innovative capacity of the established research and development model. d | The expected NME output and the number of companies are closely correlated in a nonlinear relationship that explains 95% of the changes in expected NME output by changes in the number of companies.

**Figure 2.3: Time series of the output of NME applications (circles) and approvals (bars) for the United States Food and Drug Administration (FDA)**

The European pharmaceutical industry in context

Since 2004, and even before that date, the global pharmaceutical industry has seen a consolidation of companies and the creation of huge multinational corporations. This merging of companies across the Atlantic means that it is sometimes difficult to characterize a company as "European." North America is the world’s leading market for pharmaceutical products and most new products today are launched in the United States because of the size of its market and the absence of price controls.

Meanwhile, in 2011 Europe remained the second largest global market for pharmaceutical sales. The presence of a highly-skilled workforce and robust framework for the protection of intellectual property rights (IPRs) were key factors in the decision by industry to invest €27.5 billion in R&D in Europe in 2011. The pharmaceutical industry is one of the few sectors to contribute positively to the EU’s trade balance. Its trade surplus of €48.3 billion in 2011 was the highest among the high-tech industries.

Box 2.1: Five-Cent Diabetes Pill From 1958 May Be New Cancer Drug
By Jason Gale and Andrea Gerlin - Sep 26, 2012

The next new treatment for breast, colon and prostate cancers, among others, may be a diabetes drug first approved in 1958. Metformin, the most commonly used medicine to lower blood sugar, is the subject of about 50 cancer studies globally, according to USA government clinical trial information compiled by Bloomberg. The research began after scientists found metformin prevented tumors in mice and that diabetics were less likely to develop a malignancy if they were taking the 5 cents-a-day pill than other diabetes medications. If the latest trials on breast and other tumors are successful, the drug could become a cheap weapon in the fight against a myriad of diseases including pancreatic and ovarian cancers. “The hope is that if it does show safety and efficacy, it would be available in a cost-effective way,” said Chandini Portteus, vice president of research, evaluation and scientific programs at Susan G. Komen for the Cure, a Dallas-based breast cancer advocacy group. “It would be wonderful for patients if we had something that we knew worked and was safe and low-cost.”

Further studies of metformin in cancer have been hampered by a lack of funding since large-scale trials can cost tens of millions of dollars. Metformin, which Bristol-Myers Squibb Co. (BMY) sold in the United States as Glucophage, lost patent protection years ago, meaning that manufacturers no longer reap significant profits from its sale. Pamela Goodwin, an oncologist at Toronto’s Mount Sinai Hospital, is leading a trial in 3,582 breast-cancer patients at 300 locations. Data analysis from the five-year study may start in 2016 or 2017, according to Goodwin, who said she was ready to start on the research a decade ago, but lacked financial support from companies, including one that still had a patented version. She declined to identify the company. “When they realized the results wouldn’t be available until they lost their patent, they pulled out,” said Goodwin, whose US$ 25 million study is supported by the Canadian and United States governments as well as not-for-profit groups including the Canadian Cancer Society, the Breast Cancer Research Foundation and Cancer Research UK. Apotex Inc., a Toronto-based maker of generic medicines, is supplying metformin and a placebo used in the trial.
Annual global expenditure on medicines will reach nearly US$ 1.2 trillion by 2016 (EU5 countries\(^a\), Japan, the United States, and emerging markets), up from over US$ 900 billion in 2011.\(^b\) In the developed markets, including Europe, Japan and the United States, spending is expected to decline to 57% of the global total – down from 76% in 2006. This is due to growth in emerging markets as well as the expiry of patents for a number of significant brand-name medicines, slower increases in spending on branded products, and increased cost-containment measures by payers.\(^b\)

Of these sales, however, only 7% are driven by products launched within the last five years, indicating the continued reliance of industry on more established products. From a business viewpoint, the ever-increasing cost of medicines development is an incentive for companies to invest in products likely to provide the highest rate of return on R&D investment. This leads to a somewhat conservative business model (i.e. the development of medicines against proven targets) using approaches that have already been clinically and financially successful\(^c\).

The level of investment in pharmaceutical R&D in Europe, Japan and the United States varies significantly, with the highest concentration of biopharmaceutical R&D expenditure in the United States. The latest 2011 data show pharmaceutical R&D expenditures leveling off in the United States and Europe (Figure 2.4). In 2011, a total of 49 innovative medicines were approved by the European Medicines Agency (EMA) for a range of different diseases. They include: 37 new medicines (not including medicines for rare (“orphan”) diseases), 11 new medicines for orphan diseases and one advanced-therapy medicine for the EU market (not including national authorizations).\(^b\)

The United States accounts for an estimated 38.1% of global pharmaceutical production, just ahead of Europe and well ahead of Japan. Together, these three regions account for the bulk (approximately 82%) of global pharmaceutical production by value. In 2009, the Asian region was by far the fastest growing market, with an estimated growth of 15.9%, while the growth of the North American and European markets was estimated at 5.5% and 4.8% respectively in value.

\(^a\) The EU5 countries are France, Germany, Italy, Spain and the United Kingdom.
Figure 2.4: Pharmaceutical R&D expenditure in Europe, USA and Japan (Million of national currency units*), 1990-2011

Source: European Federation of Pharmaceutical Industries and Associations: EFPIA Annual Review of 2011 and Outlook for 2012
Note: Europe: € million; USA: $ million; Japan: ¥ million × 100, (e): estimate

4 EU Framework Programmes

Although the EU Framework Programmes (FPs) only started in 1984, the evolution of European research programmes can be seen as far back as the 1950s, when the European Coal and Steel Community (ECSC) was formed. The next major collaboration was the 1957 European Atomic Energy Community (EURATOM), which encouraged research into nuclear energy. The European Community was first formed in 1967 and attempts were made to formulate a European research policy. Significantly, in the European context, research programmes have never been just about research results. It has always served some other, extra purposes, usually related to the cause of increasing European unity and building pan-European capacity. This is manifest as the importance given to ‘cohesion’ whereby priority is given to projects involving the less developed countries of the EU. Industrial competitiveness has been the other prime motivation behind European research.

The rationale to justify R&D at the European level was first agreed in 1983 in the so-called “Reisenhuber Criteria”19. In brief, European Community involvement is justified with:

- “research conducted on so vast a scale that single Member States either could not provide the necessary financial means and personnel, or could only do so with difficulty”
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- “research which would obviously benefit financially from being carried out jointly, after taking account of the additional costs inherent in all actions involving international co-operation”
- “research which, owing to the complementary nature of work carried out at national level in a given sector, would achieve significant results in the whole of the Community for problems to which solutions call for research conducted on a vast scale, particularly in a geographic sense”
- “research which contributes to the cohesion of the common market, and which promotes the unification of European science, and technology; as well as research which leads where necessary to the establishment of uniform laws and standards”

All FPs since 1992 have followed the Maastricht Treaty of February 1992, which had a significant effect on European research – notably the addition to Article 130f, which expanded Community research from the “scientific and technological bases of Community industry” to include “all the research activities deemed necessary by virtue of other Chapters of the Treaty”.20

There are several important practical and policy issues that have been raised over the years regarding the FPs.

How successful have they been and how does one measure this effectiveness? Some have taken the position that the association between the growth of the Framework Programmes and measures of EU competitiveness and technological success is far from obvious (See Section 4). The amount of money spent through this route is small relative to Member States’ research budgets or even the budgets of some European companies. The impact of other Community policies may be more important than Framework Programmes if the effect of the Framework Programmes is to discourage application of the ideas which result. Thus a regulatory directive might outweigh the benefits of Framework-funded R&D in that field.

How should future priorities be set? The issue is that there are a large number of organizations potentially involved, which creates a considerable challenge if the process is to be inclusive and open.

What should priorities be? There is, for the most part, some agreement on the main themes, but room for debate over the details.

What is the real purpose of FPs? In principle, research could be aimed at any of the following: strengthening basic research in the EU, facilitating a more equal distribution of scientific skills throughout the Community, encouraging industrial development and technology application, developing prototypes or technology demonstrators in key market sectors, encouraging a 'European' dimension to industry, through collaboration between national companies, and performing research to inform European policy. Overall, economic competitiveness will remain a dominant rationale, but other objectives such as quality of life and underpinning EU policy are also possible. b

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b A full report on the history of European Frameworks (up until the beginning of the 5th Framework) can be found at The European Union and Research—EU Framework Programmes and National Priorities (October 1996, 73 pp.) available from the Parliamentary Office of Science and Technology (POST), House of Commons, 7 Millbank, London SW1P 3JA

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In particular, the Fifth FP had a research agenda dealing with age-related diseases and disorders of high morbidity. It sought to sponsor research in the following areas:

- nervous system: stroke, Alzheimer disease and other forms of cognitive impairment, depression, Parkinson’s disease and peripheral neuropathies
- musculoskeletal system: muscular atrophy, osteoporosis and degenerative joint diseases
- urogenital system: incontinence and prostate disorders
- other gender-specific health problems
- sensory systems: visual and auditory impairments
- pain management

4.1 The Sixth and Seventh EU Framework Programmes

The Sixth FP had a particular line of research that continues to be relevant to the Priority Medicines Project. One objective was to confront the global emergency caused by the three major communicable diseases – HIV/AIDS, malaria, and tuberculosis – through the development of effective disease interventions, particularly for use in developing countries. This line of research, identified by the sixth FP, envisaged that developing countries would be significant partners and would participate directly in specific activities within the sixth FP. In particular, this aspect included support of clinical trials of promising products in, with, and for, developing countries through the European and Developing Countries Clinical Trials Partnership (EDCTP: http://www.edctp.org/) . The EDCTP is a partnership of 14 EU countries, Switzerland and Norway, and 47 sub-Saharan African countries, the purpose of which is to develop new or improved clinical interventions to combat HIV/AIDS, tuberculosis and malaria through conducting and supporting clinical trials especially phases II and III. The 2011 EDCTP Annual Report may be found in reference 20.


It consisted of four specific programmes, a “Cooperation” Programme designed to improve cooperation and networking between industry and research. For purposes of this updated Report, we note three highly relevant research areas for this FP: a) health, b) food, agriculture and biotechnology, and c) nanosciences, nanotechnologies, materials and new production methods.

The “Ideas” Programme aimed to “discover[ing] new knowledge that fundamentally changes our vision of the world and our way of life.” An autonomous Scientific Council, was created to identify priorities and scientific strategies.

The “People” Programme was designed to develop education and training for European researchers.

Finally, the “Capacities” Programme was intended to improve/increase investment in research infrastructure, creation of regional research-driven clusters and in research for the benefit of SMEs. The 7th FP financed a Joint Research Centre (JRC) designed to carry out fundamental research and provide know-how and scientific and technical support- in among other areas “life sciences and biotechnology…” for the policies of the European Union.

The Commission proposed a budget one and a half times that of the annual budget of the sixth FP. The Framework Programme was intended to have a leverage effect on national research spending, in order to achieve the objective of spending 3% of GDP on research in Europe. The following chart shows for 2007-2011 the actual FP7 expenditures in the referenced subject matter while for 2012-2013 the chart shows planned expenditure. See [http://ec.europa.eu/research/fp7/index_en.cfm?pg=budget](http://ec.europa.eu/research/fp7/index_en.cfm?pg=budget). Specifically, the total budget for Health-related activities over the duration of FP 7 is €6 billion. See [http://ec.europa.eu/research/health/health-research-intro_en.html](http://ec.europa.eu/research/health/health-research-intro_en.html). The total budget for Food, Agriculture and Biotechnology over the duration of FP7 is €1.9 million (2007 - 2013). See [http://ec.europa.eu/research/fp7/index_en.cfm?pg=food](http://ec.europa.eu/research/fp7/index_en.cfm?pg=food). The total budget for Information and Communication Technologies (ICTs) over the duration of FP7 is €9 million (2007 - 2013).

Figure 2.5: Framework Programme 7 Expenditures for 2007-2011

![FP 7 Expendures (2007-2013)](image)

4.2 Horizon 2020

This Programme departs from the tradition of numerical naming and this is specifically designed to indicate that this next Programme will be a significant departure from the previous. Horizon 2020 – the Framework Programme for Research and Innovation – is a broader concept. There had been some criticism of FP7 as lacking a strategic focus. We note FP7’s €50 billion accounted for only approximately 5% of total public research funding in the EU member states (See Appendix 2.1a). More specifically, some have asserted that FP7 research priorities have not been properly aligned with the goals set by the European Commission’s 10-year strategic plans (the Lisbon Agenda running from 2000 to 2010 and the EU2020 for 2010 to 2020. Second, it has been argued that the research and innovation funding awards have not been well coordinated. This has been suggested to lead to gaps in funding that has slowed innovation.

A big difference between FP7 and Horizon 2020 is that the latter will merge the FP with the Competitiveness and Innovation Programme (CIP – see http://ec.europa.eu/cip/) and the European Institute of Technology (EIT – see http://eit.europa.eu/) to create the ‘whole innovation chain’ approach.

We note in particular the Horizon 2020 intent to focus on so-called “Grand Societal Challenges” (See Appendix 2.1b) which included: i) health, demographic change and well-being, ii) towards more inclusive, innovative and secure societies, iii) secure, clean and efficient energy, iv) smart, green and integrated transport, v) resource efficiency and climate action, vi) food security and bioresources (See Appendix 2.1b).

The idea of “Grand Societal Challenges” sends a message that the European Commission is interested in solving major societal problems, as opposed to advancing knowledge in specific areas. This is a bold political vision which might mean some difficult choices lie ahead about what to fund and what not to fund. All programmes of Horizon 2020 (including Grand Challenges plus a focus on SMEs, ERC Grants, Marie Curie Mobility Grants and others) are intended to be supported by funding schemes to increase coordination and decrease the fragmentation of European research and innovation.

5 G10 EU Policy Environment and Pharmaceutical Innovation

5.1 The Pammolli Report and its progeny

The European pharmaceutical and chemical industry has its roots in the mid-19th century when French chemists from the dye industry expanded use of such materials to manufacture pharmaceuticals.

Over the years, the European pharmaceutical industry has become a stronghold of European industrial development. In the past two decades, however, a perception has emerged that the European pharmaceutical industry has been losing ground to that in the United States. This was strengthened by the so-called Pammolli report (named after one of its authors), a report issued in 2000 called “Global Competitiveness in Pharmaceuticals: A European Perspective” (See Appendix 2.1 of original 2004 Report).
The main finding of the Pammolli Report was that the European pharmaceutical industry had been losing competitive advantage as compared to the United States, even though large differences exist across European countries. As a whole, the Report found that Europe was “lagging behind in its ability to generate, organize, and sustain innovation processes that are increasingly expensive and organizationally complex”. In essence, competitiveness of the European pharmaceutical industry was inhibited by domestic and fragmented markets and research systems. Several variables were found to be relevant in this regard to pharmaceuticals: 1) The size and the structure of the biomedical education and research systems; 2) Some basic institutions governing labor markets for skilled researchers and managers, as well as corporate governance and finance; 3) Intellectual property rights and patent law; 4) The nature and intensity of competition on the final market.

In large part as a response to the Pammolli Report, a high level commission of the European Union (High Level Group on Innovation and Provision of Medicines-(the “G-10 Medicines Group”): (2004 Report: Appendix 2.2) was convened to provide a number of recommendations for public health policies and actions in the area of pharmaceuticals. These proposals were directed to competitiveness within the industry, pharmaceutical regulation and innovation, generic medicines and the role of patients. In July 2003, the European Commission provided its responses to the 14 wide-ranging recommendations set out in the G-10 Report. It took each recommendation of the G-10 Report and discussed how the recommendations might be taken forward and what the G-10 Group could do to facilitate the process (See 2004 Report: Annex 2.3). Significantly, these Commission recommendations were cognizant of the health issues raised by the soon-to be expanded EU. The recommendations put forward were considered in the perspective of the enlargement of the EU to central and eastern European countries.

These patterns of losing competitive advantage were confirmed for the biotechnology industry in a 2007 report.27

In 2011, a further analysis by Pammolli and colleagues confirmed that, although investment in pharmaceutical R&D has increased substantially over recent decades, there is still a lack of a corresponding increase in output in terms of the approval of new medicines, an indication of continuing challenges in therapeutic innovation.28 However, the authors also investigated potential variations in productivity with regard to the regional location of companies and found no evidence of any “productivity gap” between the United States and Europe.

5.2 Public Consultation: The future of pharmaceuticals for Human use in Europe

In August 2007, the European Commission initiated a public consultation on the future of pharmaceuticals for human use in Europe. The objective of this consultation was to “…raise awareness on the importance of ICT solutions in a future regulatory framework for pharmaceuticals, particularly in the area of safety of medicines.”29 (See Appendix 2.2a).

In brief, the majority of contributors were in agreement that issues related to globalisation of the pharmaceutical sector, the increasing fragmentation of the value chain, the functioning of the internal market in Europe, and advances in science and technology were important. Some contributors voiced concerns that patients’ access to medicines was not uniform across the EU. Tackling health inequalities, through the achievement of a genuine single market
and the development of more affordable medicines, was therefore considered to remain as a major public health issue. Many stakeholders, in particular from the industry, commented on various issues related to clinical trials which were felt to become increasingly more difficult and burdensome in terms of resources. See http://www.epha.org/a/2891).

On December 10th, 2008, the European Commission adopted a Communication and three legislative proposals based on this consultation (See http://ec.europa.eu/health/human-use/package_en.htm in addition to Updated Appendices cited below.)

One proposal was designed to provide clear rules on information provided by pharmaceutical companies on prescription-only medicines.30 (See updated Appendix 2.3)

The second legislative proposal aimed to better protect patients by strengthening the EU’s system for the safety monitoring of medicines (pharmacovigilance).31,32 (See updated Appendix 2.2b and updated Appendix 2.2c).

The third legislative proposal aimed to strengthen EU legislation to better protect EU citizens from the serious threats posed by fake medicines.33,34

5.3 Innovative Medicines Initiative (IMI)


The European Commission’s Seventh Framework Programme contributed €1 billion to the IMI research programme. That amount was matched by mainly in-kind contributions (consisting mostly of research activities) worth at least another €1 billion from member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

In 2008, grants of €123 million were handed to the most promising research projects in the areas of brain disorders, metabolic and inflammatory diseases. Since 2008, other calls for proposals covered cancer and infectious diseases. According to the IMI, these areas have been chosen because they are, primarily, important areas of “unmet medical need”. A second Call for Proposals was launched in autumn 2009. The IMI is now on their 8th call for proposals. As of June 2012, IMI is now supporting a total of 30 projects with a combined total cost of over €650 million. In the future, IMI expects to fund projects by the end of 2012 in areas related to obesity, Alzheimer Disease, drug delivery by nano-carriers, sustainable chemical drug production, the behavior of drugs in the human body, knowledge management and stem cells for drug discovery. In addition, as of May 2012, the IMI launched a call for proposals to tackle antimicrobial resistance and to speed up the delivery of new antibiotics to patients. The financial contribution from the European Community for the support of research activities is intended to match in kind contribution from EFPIA companies, whose budget is estimated to be €114 700 000. Thus the total programme is estimated to be on the order of about €220 million. See Chapter 6.1 and http://www.imi.europa.eu/content/stage-1-4.
5.4 European Medicines Agency Roadmaps

In 2005, the European Medicines Agency (EMA) developed a strategy for its work for the five years to 2010. The aims of the ‘Roadmap to 2010’ were to:

- contribute to better protection and promotion of public and animal health
- improve the regulatory environment for medicinal products
- help to stimulate innovation, research and development in the European Union (EU)

Various initiatives have been undertaken since 2005 and progress made with the implementation of the EMA Road Map has been described in two Status Reports which have been made publicly available, in May 2006 and October 2007 respectively. See http://www.emea.europa.eu/htms/general/direct/roadmap/roadmapstatus.htm.

In December 2010, the EMA published a further document setting out a strategic vision for the operation of the Agency from 2011 to 2015. This document describes three priority areas for the Agency’s work:

1. Addressing public health needs
   - Stimulating the development of medicines for areas of unmet medical need, neglected diseases and rare diseases, and for all types of medicines for veterinary use
   - Facilitating new approaches to medicine development
   - Applying a more proactive approach to public-health threats where medicines are implicated

2. Facilitating access to medicines
   - Addressing the high attrition rate during the medicine-development process
   - Reinforcing the benefit/risk-balance assessment model
   - Continuing to improve the quality and the regulatory and scientific consistency of outcome of the scientific review

3. Optimising the safe and rational use of medicines
   - Strengthening the evidence base in the post-authorization phase to enable better regulatory decision-making
   - Enhancing patient safety by avoiding unnecessary risks to patients as a result of the use of medicines
   - Becoming a reference point for information on the medicines evaluated by the Agency
   - Improving the decision-making process by taking account of patient experience

For details, including the implementation plan.


The Road Map 2015 report identifies the following drivers for the future activities of the EMA:

- Need to ensure efficient operation of the Agency’s core business
- Addressing ongoing public health needs including demographic changes, emerging public health threats, antimicrobial resistance and rapid development of new technologies
- Evaluating new and emerging science which may address unmet medical needs
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- Ensuring that the model for regulating medicines remains current and effective
- Protection of public safety
- Addressing the need for more openness and transparency and
- Addressing the impacts of globalization

More specifically, to address current and anticipated public-health needs over the next five years, the EMA intends to focus on activities relating to addressing gaps in medicines development, responding to new and emerging science and putting in place the necessary preparedness mechanisms to respond to emerging health threats.

In the context of this Updated Report, three main ‘gaps’ in drug development have been identified by the EMA; neglected and rare diseases, specific activities relating to aging populations and the need to address the pipeline gap for new antibiotics. Each of these EMA priorities has a counterpart in the present Update.

The focus of efforts to address the challenges of new and emerging science will include efforts to enhance liaison between approaches to drug and diagnostic development, facilitation of biomarkers and the science supporting the development of more personalised medicines.

With regard to its responsiveness to public-health threats, the EMA intends to build on experience with influenza pandemic preparedness to assist the Commission in the development of a strategy with European partners to ensure a coordinated European response. The EMA also intends to intensify work on a European and international perspective to minimise the risk of antimicrobial resistance (AMR) arising from the use of both human and veterinary medicines within the framework of Community and international activities including the Transatlantic Taskforce on AMR established based on conclusions of the 2009 EU-US summit (See Chapter 6.1)

5.5 The Barcelona European Council: The “3% Solution”

In March 2002, the European Council, partly in response to the Pammolli report, officially called for action to increase public and private investment in research and technological development. To this end, the EC asserted that investment in research (both public and private) should rise from 1.9% to 3% of GDP in the European Union by 2010. The share allocated to private funding should rise to two-thirds of the total. The thesis is that there is a “research gap” in investment causing less attractive conditions for private investment in public and private research in Europe. Based on consultations arising from this initiative, the EC discovered that although many EU companies were strategizing for global development, they were not planning new research investment in the European Union but rather in other regions that they deem more attractive, such as the United States and some Asian countries.

The EC recognized the value of public funding insofar as links to industry are emphasized. There are explicit directives in the Report to improve the effectiveness of public support for research and innovation and redirect public resources towards research and innovation. For instance, the EU stated a desire to improve links between public research institutions and the private sector and “...such partnership offers a potentially powerful tool to make investment in research more attractive to business while also benefiting public research.”
The sense of this “3%” initiative, given that the share allocated to private versus public funding is meant to rise to 2:1, is that research and innovation should be primarily directed towards the private sector. There is a role for publicly-funded institutions to deal with “research gaps” as well as failure of the private sector to innovate in certain areas (e.g., “neglected” diseases of developing countries exclusive of HIV, malaria and TB, medicines specifically geared towards children, women and the elderly).

5.6 “Europe 2020 Strategy” for Growth

In June 2010, the European Commission launched the "Europe 2020 Strategy" which is a strategy for economic growth of the EU. The strategy sets several targets which define where the EU should be by 2020 and which progress can be tracked. The most relevant for the present update is the continuing target that 3% of the EU’s GDP should be invested in R&D. We also note that an education and training target is likely relevant for the continued sustainability of pharmaceutical R&D, namely that “[T]he share of early school leavers should be under 10% and at least 40% of the younger generation should have a tertiary degree or diploma.” (See updated Appendix 2.4, page 3).

6 The United States Policy Environment

6.1 NIH Common Fund and NIH Roadmap for Medical Research

The NIH Common Fund was enacted into law by Congress through the 2006 NIH Reform Act to support cross-cutting, trans-NIH programmes that require participation by at least two NIH Institutes or Centers (ICs) or would otherwise benefit from strategic planning and coordination. The requirements for the Common Fund encourage collaboration across the ICs while providing the NIH with flexibility to determine priorities for Common Fund support. To date, the Common Fund has been used to support a series of short term, exceptionally high impact, trans-NIH programmes known collectively as the NIH Roadmap for Medical Research (http://commonfund.nih.gov/). See updated Appendix 2.5.

Roadmap programmes span all areas of health and disease research and boundaries of NIH Institutes and Centers (ICs). These are programmes that might not otherwise be supported by the NIH ICs because of their scope or because they are inherently risky. Roadmap Programmes are expected to have exceptionally high potential to transform the manner in which biomedical research is conducted. They are also expected to be short term, 5–10 year programmes. The annual Common Fund budget was US$ 498 million in 2008. To date, the Common Fund has been used exclusively to support the Roadmap programme.

Initiatives funded through the Roadmap/Common Fund fit into one or more of these major themes and address specific roadblocks or gaps to:

- Foster high-risk/high-reward research
- Enable the development of transformative tools and methodologies
- Fill fundamental knowledge gaps
- Change academic culture to foster collaboration
Many of the programmes have achieved significant research advances. There are over 20 programmes currently in operation (http://commonfund.nih.gov/initiativeslist.aspx) ranging from nanomedicine (http://commonfund.nih.gov/nanomedicine) to global health (http://commonfund.nih.gov/globalhealth).

See http://commonfund.nih.gov/grants/fundedresearch.aspx for a list of current (2012) funding opportunities and funded projects. Since 2011, the NIH Common Fund has essentially been level funded at about US$ 544 million per year (See updated Appendix 2.5).

Criticism of Roadmap and Defense

As soon as the 2006 NIH Roadmap was presented and in the face of governmental cut-backs in general, a seemingly lone critic asserted that the NIH should rely more heavily on pharmaceutical companies to fund large clinical trials in order to reallocate the relatively more scarce NIH funds to basic science grants (called “R01 grants” in the U.S.A.) See reference 44 and 45. Representatives of 50 leading academic medical centers focusing on clinical research responded arguing that the pharmaceutical industry must focus on profit-generating opportunities which is the “… fundamental covenant with their investors” and therefore they cannot be qualified to deal with “… sustaining the issues specific to academic science.”

6.2 FDA Roadmap/Critical Path

In its 2006 Critical Path Report, the FDA presented its diagnosis of the scientific challenges underlying the problem in the medical product pipeline problem where innovative medicines were not reaching patients. The report then laid out a path forward, beginning with extensive outreach and consultation with public and private stakeholders.

The FDA has since developed a “Critical Path Opportunities List” in six areas. Two areas for improving medical product development are biomarker development (Topic 1) and streamlining clinical trials (Topic 2). The application of mathematics, statistics, and computational analysis to biological information—bioinformatics (Topic 3)—is a third challenge area. Tools that help identify and analyze critical product attributes hold the promise of improving both efficiency and quality in manufacturing (Topic 4). The FDA also believes new antibiotics and countermeasures to combat emerging infections and bioterrorism (Topic 5) are needed. Developing therapies for children and adolescents (Topic 6) is the final challenge identified. See http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/default.htm for a list of Critical Path publications and reports. A summary report for 2010 can be found at Updated Appendix 2.6a: Critical Path Report.

Most recently, the FDA produced a strategic plan, called "Strategic Priorities 2011–2015: Responding to the Public Health Challenges of the 21st Century". See updated Appendix 2.6b. The FDA has selected five cross-cutting areas to serve as strategic priorities over the next five years. These include efforts to: 1) Advance Regulatory Science and Innovation; 2) Strengthen the Safety and Integrity of the Global Supply Chain; 3) Strengthen Compliance and Enforcement Activities to Support Public Health; 4) Address the Unmet Public Health Needs of Special Populations; and 5) Advance Medical Countermeasures and Emergency Preparedness.
The FDA plans to recruit more scientists and to work with other science agencies as well as academia. Another priority is improving safety in the global food and drug supply chain, to more effectively enforce FDA laws and regulation in large part because the FDA still lacks authority to order recalls for medical devices and drugs on its own. If manufacturers or distributors refuse to comply with voluntary requests, the FDA has to seek court orders to enforce compliance.

This document also highlighted a major, and continuing, problem in clinical trials: women, minorities, and children are historically under-represented making questions about efficacy and safety go unanswered in those populations. Lastly, the agency promised to support the Obama administration’s plan to invest nearly $2 billion in measures to counter pandemic influenza, bioterrorism and other emergencies. See Appendix 2.6b.

As noted in the original Report, the FDA Critical Path Report fails to address post-market authorization activities.

7 Global initiatives

In March 2010 the European Commission issued a communication on The EU Role in Global Health. The Communication highlights that the EU should apply the common values and principles of *solidarity towards equitable and universal coverage of quality health services* in all external and internal policies and actions. This would achieved through democratic and inclusive governance, an emphasis on universal coverage and coherence between relevant EU policies related to global health. With regard to research the communication stresses that research should benefit all people and that the EU Research Framework Programs should continue to give priority to actions which tackle global health challenges.

On 26 May 2012, the WHO World Health Assembly (WHA) adopted a resolution calling for an inter-governmental meeting (scheduled for November 2012) to examine in depth the proposals made in April in the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (see Background Paper Chapter 3) established in 2010 under Resolution WHA63.23. Such proposals included: open approaches to R&D; pooled funds; direct grants to companies in developing countries; prizes for milestones and end-products; and patent pools. One of the recommendation of the Working Group was to start multilateral negotiations for the possible adoption of a binding convention on health R&D.

In November 2012, a three-day closed door meeting resulted in agreement by WHO Member States to endorse a strategic work plan that includes proposals on the coordination, financing and monitoring of R&D expenditures.

8 Objectives of Update to Priority Medicines Project

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

Nonetheless, for many diseases, there exists a “pharmaceutical gap” between the burden of disease and a clinically effective medicine. Pharmaceutical innovation, such as the creation of new chemical entities, can fill these “gaps” but, from a public health viewpoint, “innovation” can include many other different options: modifications of known medicines; development of less invasive administration routes; use of simpler administration schedules. It is one objective of this Project to prepare a public-health-based medicines development agenda, for support by the EU in the immediate near future. The document is intended as a guide for policy making, not as a guide to researchers or clinicians. In this regard, the Updated Report uses the systematic methodology of the original Report that allows interested parties to gain insight into what constitutes a “pharmaceutical gap”.

We have undertaken an updated analysis of the burden of disease in Europe and the world and have reviewed the efficacy of certain existing pharmaceutical interventions for these diseases. Based on this, we have developed a list of candidate conditions for which additional in-depth review of pharmaceutical intervention is justified. Based on our list of candidates, we performed in-depth studies of diseases that are on our list of candidates.

The Project will also attempt to identify needs regarding special patient groups and better delivery mechanisms and formulations of existing preventive and therapeutic medicines. We also report on different aspects of promoting pharmaceutical innovation through public-private partnerships, addressing regulatory barriers, and involving patients and citizens in priority-setting.

The original proposals for this Project can be found in Annex 2.1 and an expanded version in Annex 2.2.

This project is not about improving access to medicines through improving the efficiency of the health care delivery system.\d It is restricted to investigating EU pharmaceutical innovation from a public health viewpoint.

References


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


13 Nature Reviews Drug Discovery 8, 959-968 (December 2009) | doi:10.1038/nrd2961 Lessons from 60 years of pharmaceutical innovation Bernard Munos


21 European Commission, Research and Innovation, FP7, Budgets. Available at http://ec.europa.eu/research/fp7/index_en.cfm?pg=budget

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34 Citizen’s Summary; Legal proposal on measures preventing the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source. Available at http://ec.europa.eu/health/files/counterf_par_trade/conterfeit_doc/citizens_summary_counterfeiting_en.pdf


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43 NIH Research Project Grant Program (R01). Available at [http://grants.nih.gov/grants/funding/r01.htm](http://grants.nih.gov/grants/funding/r01.htm)


49 Critical Path Reports. US Food and Drug Administration. Available at [http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/default.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/default.htm)


Appendices


Appendix 2.1b  Presentation at the Stakeholder’s workshop –Common strategic framework or research and innovation –resource efficiency and climate challenge, European Commission, Brussels 21 June 2011

Appendix 2.2a  The future of pharmaceuticals for human use in Europe, Making Europe a hub for safe and innovative medicines, Outcome of the public consultation, 2008. European Commission

Appendix 2.2b  MEMO/Brussels, 10 December 2008, Strengthening pharmacovigilance to reduce adverse effects of medicines

Appendix 2.2c  Citizen’s Summary, Legal proposals on pharmacovigilance

Appendix 2.3  Amended proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL Amending Directive 2001/83/EC, as regards information to the general public on medicinal products subject to medical prescription and as regards pharmacovigilance European Commission, 2011.


Appendix 2.5  Department of Health and Human Services, National Institutes of Health. Common Fund, FY 2013 Budget.

Appendix 2.6a  Critical Path Initiative, report on projects receiving critical path support. Siscal Year 2010 report. FDA.

Appendix 2.6b  Strategic Priorities 2010-2015. Responding to the public health challenges of the 21st century. FDA.