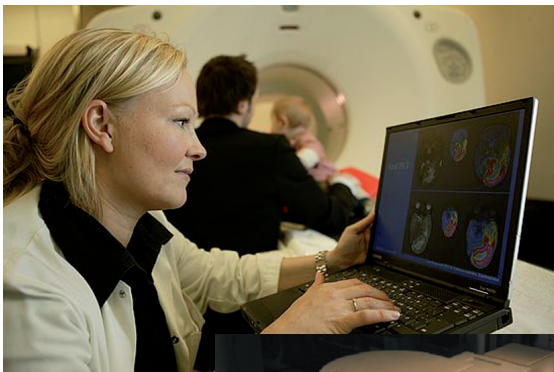


Present Status and Future Strategy for Medical Research in Europe



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Executive Summary

This 2007 White Paper from The European Medical Research Councils **“Present Status and Future Strategy for Medical Research in Europe”** aims to strengthen and improve European medical research, which in turn will result in better healthcare and improved human welfare. In Europe and in the rest of the world we are facing rapid changes in society with globalisation, new emerging and rapidly spreading infectious diseases, changed disease patterns with treatment-resistant tuberculosis, rapid and dramatic climate changes and, in Europe, a changed demography with an ageing population. Medical research is essential to cope with these future challenges. Furthermore, new knowledge in the field of medical science is important to facilitate greater success for the European medical industry.

We propose that the present level of funding for medical research across Europe is increased, and that there is enhanced collaboration between European nations and institutions. Funding should be distributed in competition through peer review on the basis of scientific excellence. Collaboration within Europe and worldwide, with the sharing of research and results, is essential for ensuring that European research can make a real difference to the health and wealth of its people. This will create a stronger medical research base, and provide society with the necessary scientific tools to meet the serious challenges facing us in the coming decades. Increased funding for medical research in Europe will, in addition, help to fulfil the recommendations of the EC Green Paper which envisions Europe as a leading knowledge-based society.

A comprehensive analysis of funding shows that the USA spends significantly more on medical research than does Europe. Relative to GDP (gross domestic product) the USA non-market sector spending on biomedical research and development in 2004 (the most recent figures available) was between 0.37 and 0.40 % compared with 0.17 % for the original 15 EU countries (EU15) in the same year. If all the EU countries were used for comparison the difference would be even more marked. The USA thus spends more than twice as much as Europe relative to GDP, and almost three times as much when measured relative to the size of the respective populations.

A bibliometric analysis of the output of medical research shows that *per capita*, the USA produces roughly one paper more per 10,000 inhabitants than does Europe (the output per 10,000 inhabitants increased from 3.2 in 1996 to 3.9 in 2005 in Europe compared with a change from 4.4 to 4.9 in the USA over the same period). The total number of citations to US publications between 1996 and 2003 greatly exceeded the number of citations to EU15 publications during the same period. The share of the world's citations to biomedical publications remained about 50% for the USA and 40% for the EU15 in the study period. This may be partially due to the positive English language bias in citation databases, but may also be due to a quality difference in favour of the USA.

We propose to use “best practice” for medical research in Europe, as described in the tool box below. Collaboration is the key-word, with a focus on strong basic research, strong clinical research, and strong translational research, bringing basic knowledge into clinical practice and *vice versa*. All three elements need to be facilitated by interdisciplinary approaches and through public-private partnerships. Career track schemes that provide attractive opportunities for researchers are essential. Research must be conducted according to the highest ethical standards, and appropriate tools of governance must be in place to prevent scientific misconduct. Europe should invest in national and European research infrastructure, as indicated in the ESFRI Roadmap. We propose that EC and national regulations that impact on biomedical research should be made as simple as possible, so that research is facilitated and not impeded. Partnership is needed in the EU among institutions. Along with improvement for the original EU members, investment should be made in technology, infrastructure and employees in the new EU member states in order to eliminate the differences between the original and new countries and to enable new member states to achieve their enormous intellectual potential. This will create an optimal environment for medical research across the whole Europe.

If funding for medical research in Europe is doubled within the next 10 years, and this is combined with the implementation of “best practice”

Executive Summary

for collaboration and organisation of medical research, there will be major benefits for European society, with a better health, welfare and hospital treatment, and a thriving medical industry. It is well documented that investment in medical research reaps large returns for society, which justifies the interventions we are proposing.

The EMRC has an important role in the future development of medical research in Europe through its science policy and through dialogue with the European Commission, the European Research Council, learned societies, universities and academic medical centres. We firmly believe that a concerted and collaborative effort to strengthen and improve European medical research will have a positive impact for health and welfare in Europe and the rest of the world, and with the publication our new 2007 White Paper **“Present Status and Future Strategy for Medical Research in Europe”** we invite debate and action to bring our proposals to fruition.

Recommendations for strengthening medical research in Europe

1. Implementation of “best practice” for funding and performing medical research (see tool box).
2. Collaboration via EMRC and its Membership Organisations and EC, ERC, COST, the scientific societies, the medical journals and the university and academic medical centres to enhance collaboration and sharing of research and results.
3. Revision of EC Directives related to medical research to facilitate research.
4. Endorsement of the EMRC statement on equal opportunities for performing research: “The EMRC advocates equal opportunities in all aspects of medical research – regardless of age, gender, origin, profession, race, religion, or sexual orientation.”
5. A doubling of public funding of medical research in Europe within the next 10 years – to a minimum level of 0.25 % of GDP and the necessity for sustaining a steady growth above inflation in the years to come after the doubling.

Tool Box: “Best Practice” for medical research in Europe:

Primary goals:

- Strong basic research
- Strong clinical research
- Strong translational research: bringing basic research knowledge into clinical practice, and *vice versa*
-- all three of the above being facilitated by interdisciplinary research and public-private partnerships

Tools to reach these goals: people

- Career track schemes with attractive possibilities for researchers taking advantage of co-funding strategy
- European Medical Scientific Training Programme (EMSTP) for physicians and scientists scaling up existing successful initiatives
- The highest level of research ethics, and no scientific misconduct

Tools to reach these goals: research infrastructure

- Investment in national and European research infrastructure – covering the whole range from laboratory equipment in basic science labs and research facilities in hospitals, to the largest pan-European infrastructures, as outlined in the ESFRI Roadmap
- Launch a call for proposals to directly support on a highly competitive basis a league of top performing biomedical research centres of excellence, integrated into regional clusters
- Post-genomic clinical medicine
- Intelligent and coordinated use of Information Technology (IT)
- EC and national regulatory issues for clinical research adapted to facilitate research

Tools to reach these goals: research funding

- Adequate research funding – distributed on the basis of scientific excellence and through peer review
- Common criteria and methods for the evaluation of research outcomes

Tools to reach these goals: societal means

- Globalisation and collaboration: sharing of research and results
- Public engagement about medical research and its possible impacts
- Preparedness for the future



Preface

The aim of this White Paper from The European Medical Research Councils (EMRC) is to strengthen and improve European medical research – for creating new knowledge, better practice of medicine and an improvement in human health and welfare.

The White Paper may be read as a coordinated and consensus reply from the European Medical Research Councils to the EC Green Paper¹, ‘The European Research Area: New Perspectives’, which highlighted that research is a cornerstone for a European ‘knowledge society’.

The White Paper was developed during two round-table meetings in Paris on May 28 and July 20, 2007 hosted by the EMRC and endorsed at the EMRC Plenary Meeting in October 2007.

The return on investment in medical research are enormous for society, and proper funding for medical research in Europe will lead to better health, welfare and economic prosperity. We hope that this White Paper will lead to a debate followed by actions to create improved conditions for medical research in Europe, and thereby secure for European patients and citizens the benefits from significantly improved health and welfare in the future.

A very warm thank you to the White Paper authors: Prof. Håkan Billig, VR, Sweden; Prof. Colin Blakemore, MRC, UK; Prof. Roger Bouillon, FWO, Belgium; Prof. Christian Bréchet, Inserm, France; Prof. Arturo Brunetti, CNR, Italy; Prof. Agnès Gruart, MEC, Spain; Dr. Tony Peatfield, MRC, UK; Prof. Martin Röllinghoff, DFG, Germany; Prof. Jürgen Schölmerich, Regensburg Univ. & DFG, Germany; and Prof. Eero Vasar, EAS, Estonia.

Grateful thanks are also due to Drs Michael Stolpe, Van Bui, Gisela Hostenkamp and Robert Poppe, The Kiel Institute for the World Economy, Germany, as well as the national and international experts listed in the appendix for the superb gathering and analysis of data on biomedical research funding, and to Dr. Wolfgang Glänzel and Dr. Koenraad Debackere, Managerial Economics, Strategy and Innovation (MSI), Leuven, Belgium, and Dr. Martin Meyer, SPRU, Univ. of Sussex, UK for excellent assistance in data collection and evaluation of European biomedical research performance.

A special warm thank you to Dr. Carole Moquin-Patthey, Head the EMRC Unit in Strasbourg, France and to her assistant Julien Weber for excellent organisation of this White Paper process.

We are grateful also to Dr. Elias Zerhouni and his team at The National Institutes of Health (NIH), USA, for their very valuable comments to the White Paper.

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Chair of the EMRC**

¹ EC Green Paper The European Research Area: New perspectives’ Brussels 4 April 2007
Download at: http://ec.europa.eu/research/era/pdf/era_gp_final_en.pdf

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1. Introduction: “The special case of medicine”

This EMRC 2007 White Paper “Present Status and Future Strategy for Medical Research in Europe” aims to strengthen and improve European medical research – for better healthcare and improved human welfare, to create new knowledge in the field of medical science, and to facilitate greater success for the European medical industry.

Stronger medical research in Europe will have positive consequences for European welfare, as the benefits from medical research to society are substantial, with a many-fold return from investments in medical research. Healthcare costs have increased substantially in the last 10–15 years, but public funding of medical research in Europe has only increased modestly in comparison. As has been voiced in the USA², better funding of medical research and its translation towards evidence-based medicine will be important for improving healthcare systems, and thereby contributing to the reduction of healthcare costs in the future.

Preparedness is a key word for our future development in Europe. We are facing a rapidly changing society, with globalisation, new emerging and rapidly spreading infectious diseases, bioterrorism, and changes in disease patterns in Europe and in the rest of the world. Tuberculosis is increasing in Europe, with new and rapidly changing microbial resistance patterns, leading to treatment resistance. Rapid and dramatic climate changes anticipated in the near future will modify disease patterns, and represent a major challenge. A changed demography with an ageing population will result in an increased demand for healthcare. Neurodegenerative disorders and depression will increase, and an epidemic of obesity and the metabolic syndrome will be another substantial challenge with diabetes and all the related side-effects: cardiovascular and kidney diseases, blindness, and bone and joint problems. The post-modern global society with increased societal stress, fear of the future, and a changing European demography will lead to grand challenges in the area of mental health-related diseases. **Medical research is essential to cope with these future challenges in the best and most intelligent way.**

Biomedical research should be instrumental in accompanying the paradigm shift from the present healthcare system into a new era, where prevention of disease and healthy ageing are the primary goals.

The EC Green Paper states: “ERA is essential to making Europe a leading knowledge society and thus creating the conditions for long-term prosperity, a society where research, education, training and innovation are fully mobilised to fulfil the economic, social and environmental ambitions of the EU and the expectations of its citizens.” This should be viewed in the context of the Lisbon strategy, agreed by Member States in 2002, which stated that “overall spending on R&D and innovation in the Union should be increased with the aim approaching 3% of GDP by 2010, with two-thirds of this investment coming from private sector”^{3,4}. Science is global, and stronger and better European medical research will yield benefits for Europe, as well as more widely. Overall it will help improve welfare for the whole world.

Research is on the European and national political agendas. Dr. Janez Potočnik, Commissioner of Research and Science at the European Commission, highlighted that “What we need and what we want is an attractive Europe, with exciting research opportunities in the scientific fields of the future, with the human resources and capacities optimised to match our ambitions; with a society that is aware and supportive of research”. The new British Prime Minister Gordon Brown is quoted in *Science* 6th July 2007: “The government’s long-term vision is to make Britain one of the best places in the world for science, research and innovation”⁵. One of the first acts the new French President, Nicolas Sarkozy, was to create a new ministry whose responsibility includes both research and higher education. In Germany, under the leadership of *Bundeskanzlerin* Dr. Angela Merkel, herself a scientist, the ‘Excellence Initiative’ has already been underway for two years⁶.

Medical research is special, as the outcome of the research produces not only new knowledge, science and innovation (as for other research

² Zerhouni, EA., (2007). Fiscal year 2008 Budget Request Witness appearing before the Senate Subcommittee on Labor-HHS-Education Appropriation: <http://www.nih.gov/about/director/budgetrequest/fy2008directorssenatebudgetrequest.htm>

³ Presidency conclusions Barcelona 15 & 16 March 2002: http://ec.europa.eu/invest-in-research/pdf/download_en/barcelona_european_council.pdf

⁴ More research for Europe Towards 3% of GDP <http://ec.europa.eu/invest-in-research/pdf/499/en.pdf>

⁵ Clery, D. Science gets new home in U.K. Government. *Science* July 2007; 317: 28.

⁶ On 23 June 2005 the German federal and state governments

agreed on an initiative to promote top-level research in Germany. The Excellence Initiative aims to strengthen science and research in Germany in the long term, improve its international competitiveness and raise the profile of the top performers in academia and research. The total budget of the initiative will be €1.9 billion for the period 2006 through 2011, which will be split between three lines of funding: i) Graduate schools to promote young researchers; ii) Clusters of Excellence to promote world-class research; iii) Institutional strategies to promote top-level university research http://www.dfg.de/en/research_funding/coordinated_programmes/excellence_initiative/general_information.html

1. Introduction: “The special case of medicine”

areas), but can also rapidly be translated into better ways of preventing disease and improving healthcare. The benefit for patients is often both immediate and invaluable.

Medical research should be used to transform the present healthcare system into one that is focused much more on prevention. This will come about through the intelligent and collaborative use of the exploding amount of new knowledge on genetic analysis, biomarkers and risk assessment, thereby leading to better and longer lives for people globally. All this new information can be harnessed to produce a new type of “post-genomic” personalised medicine, where interventions will focus on prevention and early diagnosis, rather than, as now, on diagnosis, treatment and rehabilitation after the onset of disease.

This White Paper consists of a discussion about the important positive impact of medical research on health, welfare and the European economy, followed by an assessment of funding levels for medical research in Europe compared to USA and the rest of the world. There is then an evaluation of the scientific and societal outcomes of European medical research, again compared to the rest of the world. The paper concludes with recommendations about how to improve and strengthen medical research in Europe through better funding and use of “best practice”.

2. The positive outcomes of medical research

The most important outcomes of medical research are better prevention strategies, better treatments for individuals, and broader health and societal and economic benefits. Medical research plays a key role in improving health and prosperity. New studies applying micro- and macro-economic models for accessing the socio-economic effects of research have shown very high returns on investment into medical research. A recent study⁷ showed a more than four-fold return on investment in randomised clinical trials funded by the US National Institute of Neurological Disorders and Stroke. An Australian study showed an eight-fold return on cardiovascular research, a six-fold return on respiratory medical research, and a five-fold return on digestive disease research⁸. The UK Government Science and Innovation Framework 2004 concluded that innovation in science and technology has driven the increasing living standards in developing countries over many years, and that investment in research has had a consistently positive impact on long-term national productivity and growth^{9,10}.

Policy-makers and the tax-paying public need to understand the benefits that arise from investment in medical research in order to make well-informed decisions about funding of medical research. In Europe and the USA, spending on health-related R&D is respectively 0.14% and 0.33% of GDP¹¹, which is very small compared to current and likely future health expenditure.

Recent economic studies predict a rising demand for healthcare at least until the middle of the 21st century. An influential article¹² has shown that rising incomes alone could lead to a doubling in the efficient share of health spending in GDP in the coming decades, even without the degree of population ageing that is forecast. But population ageing will of course create an additional unprecedented demand for the findings, better practices, new treatments and technologies from

medical research. These predictions are based on the empirical observation that as people get richer and consumption rises, additional consumption of material goods becomes relatively less valuable, but the value of additional years of life does not decline. The optimal composition of total spending shifts towards health, and the efficient share of health in GDP will grow as long as per capita incomes rise. For the USA, the authors predicted an optimal health share in GDP of more than 30 % by the middle of the 21st century.

One of the best-known attempts to describe the value of medical research to society in economic terms is a US-study sponsored by The Mary Woodward Lasker Charitable Trust¹³. Improvements in health were found to account for almost half of the gain in American living standards in the previous fifty years. The decline in deaths in the US between 1972 and 1992 from cardiovascular disease and stroke was worth more than USD 1.5 trillion per year to the US economy. Assuming that only one-third of this gain came from medical research, the return on investment in research (USD 500 billion per year) was twenty times greater than annual spending on medical research. An investment of USD 100 billion in research would yield USD 935 billion in societal gain.

At present European medical industries invest more in US-based research than in Europe-based research; this is a sign that European medical R&D could perform better^{14,15}. It has been shown that resources used in the pharmaceutical industry produce greater economic benefits than if they were employed elsewhere, for example in manufacturing. Private-public partnerships, with collaboration between industry/academia/hospitals/charities, are an important future means for enhancing prosperity in Europe. In the US, it has been suggested that 500,000 jobs in the pharmaceutical industry would not exist if the

⁷ Johnston SC, Rotenberg JD, Katrak S, Smith WS, Elkins JS. Effect of a US National Institutes of Health Programme of clinical trials on public health costs. *Lancet* 2006; 367: 1319-1327.

⁸ 'Exceptional returns, the value of investing in health R&D in Australia'. Prepared for The Australian Society for Medical Research by Access Economics; Canberra, September 2003. Download at: http://www.researchaustralia.com.au/files/Access_Economics_Exceptional_Returns.pdf

⁹ Medical research: assessing the benefits to society. A report by the UK Evaluation Forum, supported by the Academy of Medical Sciences, Medical Research Council and Wellcome Trust, May 2006

¹⁰ Blakemore C, Davidson J. Putting value on medical research. *Lancet* 2006;367: 1293-1295.

¹¹ See Figure 1 in Chapter 3.

¹² Hall RE, Jones CI. The value of life and the rise in health spending. *The Quarterly Journal of Economics* February 2007;122:39-72.

¹³ Funding First. Exceptional Returns: The Economic Value of America's Investment in Medical Research. Mary Woodward Lasker Charitable Trust: New York, NY 2000. Download at: <http://www.laskerfoundation.org/reports/pdf/exceptional.pdf>

¹⁴ Science & innovation investment framework 2004-2014: next steps. A report by The Department of Health, the Department for education & skills, the DTI and HM Treasury, March 2006. Download at: http://www.hm-treasury.gov.uk/media/7/8/bud06_science_332v1.pdf

¹⁵ The Pharmaceutical Industry in Figures. A Report of the European Federation of Pharmaceutical Industries and Associations (EFPIA), June 2006.

2. The positive outcomes of medical research

industry were not standing on the shoulders of public funding and academic performance¹⁶. This requires a well-functioning public medical research base and a positive attitude towards private–public partnership.

Continuous and substantial funding in specific research areas has led to dramatic improvements, e.g. for children with cancer, where the cure rate is now well above 75%; this can be ascribed to the medical research efforts in paediatric oncology over the last fifty years¹⁷. Strong research efforts building on basic science knowledge have led to the novel effective vaccine against human papilloma virus (HPV), which can prevent cervical cancer¹⁸. On the other hand, an under-researched area, such as respiratory diseases, has failed to come up with similar improvements for patients with lung diseases¹⁹.

Assessing returns on medical research in economic terms in Europe is difficult and should become a research area in its own right. It is extremely difficult to evaluate the societal outcome of medical research, as it is a complex, slow and incremental process. Likewise, it is a demanding task to ensure that all areas of expenditure and benefits for human health are recognised. There is a time-lag between research and tangible outcomes, and it is difficult to trace the role of individual research contributions. A commonly accepted methodology for how to evaluate outcomes of research funding both from public funding and from private charities needs to be developed, and both public funding organisations and private charities supporting medical research

should employ such methods for assessment of the outcomes of their research funding.

Greater spending on medical research and development today is a necessary investment for reducing the healthcare costs of tomorrow. A research environment that contributes to the health and wealth of the European nations is essential, as new ideas, new evidence, and new products provide the necessary base for more effective and more efficient healthcare systems. It will secure economic growth through a healthier workforce and by providing an attractive environment for investment by pharmaceutical and biotechnology companies.

Research is an international endeavour and the product of many different actors working over often long periods. If improved, European medical research will give further benefit to societies globally. The essential starting point for success is the selection of which research to support. Investment in poor quality basic ideas will generate useless findings. Badly designed clinical trials or epidemiological studies will produce unreliable or even harmful results and, in that they involve the participation of people, would be unethical. In contrast to this, the benefits to society of investment in excellent medical research are enormous, and therefore worth investing in.

¹⁶ Rosenberg L. Exceptional economic returns on investments in medical research. *The Medical Journal of Australia* 2002;177:368-371.

¹⁷ Pui CH, Cheng C, Leung W et al. Extended follow-up of long-time survivors of childhood acute lymphoblastic leukemia. *New England Journal of Medicine* 2003;349:640-649.

¹⁸ HPV and HPV Vaccine. Information for Health-care providers. CDC, Center for Disease Control & Prevention, USA. August 2006. Download at: <http://www.cdc.gov/std/hpv/hpv-vacc-hcp-3-pages-hi-res.pdf>

¹⁹ Blakemore C, Davidson J. Putting value on medical research. *Lancet* 2006;367:1293-1295.

3. Medical research funding in Europe and globally

In this chapter we try to find and compare data for medical research funding in Europe and globally. International comparisons of funding for medical research are plagued by conceptual and technical problems. Conceptually, we are interested primarily in knowledge about public funding relative to relevant measures of country size and economy, and we therefore report medical research funding relative to countries' gross domestic product (GDP). What matters is, however, the amount of resources that go into medical research, such as hours worked by research scientists, the utilisation of scientific infrastructure and all forms of research-specific consumables. To consider only monetary inputs may conceal important qualitative and quantitative differences between countries. For example, the stock of knowledge used as an input to generate further knowledge, varies widely. Moreover, changes in relative input prices limit the comparability of aggregate expenditure data internationally and across time, especially where a biomedical research price deflator is absent. Linking inputs to research output raises further issues: the efficiency of medical research varies with the extent to which countries exploit economies of scale and with appropriability²⁰ conditions, such as intellectual property rights, that determine private research incentives.

In addition to generating new knowledge, medical research may endow countries with absorptive capacity for existing medical knowledge, including the translation of international research advances into better healthcare practice at home. The development and application of evidence-based medicine and treatment guidelines for specific diseases requires the presence of medical researchers who are trained in the latest methods, knowledgeable about all relevant research advances worldwide, and at the same time familiar with local epidemiological conditions in the community they serve.

Technical problems in measuring medical research funding arise because the relevant definitions of research cannot fully keep pace with the changing scope, evolving science base

and rapid proliferation of research methods and technologies. International standards for the classification of research activities, for example provided by the so-called Frascati Manual²¹, are inevitably incomplete and largely rely on voluntary adherence. The two main sources of internationally comparable data on health-related research and development (R&D), Eurostat and the OECD, report research expenditures by sectors of performer and by the funding bodies involved. The data presented below are from the joint annual Eurostat/OECD survey that asks performers how much they actually spent on R&D in the preceding year and asks funders how much they have committed to R&D for the current year, and data from the USA published in peer review journals, as recommended by the NIH.

We used performer-reported data to compare the aggregates of all intramural expenditure on biomedical R&D performed in the government, higher education and private non-profit sectors, collectively known as the 'non-market R&D sectors'. Care has been taken to minimise problems arising, inter alia, from national traditions of classifying differently the human health-related parts of multifarious research activities, particularly in the field of biological research. An important advantage of performer-reports is that they include funding not only from national governments, but from all sources of R&D funds flowing into the domestic non-market sector, including funds from industry and from abroad, such as disbursements in the European Commission's Research Framework Programmes.

However, as a first look at national government priorities, we have used funder-reported data that compare government budget appropriations for health-related R&D, irrespective of the sector of performance. The difficulty here was to identify all relevant budget items and to measure or estimate their R&D content in terms of funding. The OECD and Eurostat databases²² use a breakdown by socio-economic objective (SEO) for this purpose. Besides the *protection and improvement of human health*, the relevant socio-economic objectives comprise the medical science components of

²⁰ The conditions surrounding an invention that enables the capture of the value of an innovation. Some amount of appropriability is necessary to make more money than the cost of R&D. Strategies to ensure appropriability include patents, branding, gaining lead time and exploiting a learning curve advantage (legal, technical, or strategic). Appropriability can be considered part of the competitive advantage and is part of the defensibility and sustainability of a venture.

Retrieved from "<http://andrewhargadon.com/wiki/index.php?title=Appropriability>"

²¹ OECD (2002). Frascati Manual - Proposed Standard Practice for Surveys on Research and Experimental Development. Paris: OECD.

²² The OECD R&D database is at: <http://caliban.sourceoecd.org/vl=7429255/cl=24/nw=1/rpsv/cw/vhosts/oecdstats/16081242/v209n1/contp1-1.htm>

The Eurostat R&D database is at: http://epp.eurostat.ec.europa.eu/portal/page?_pageid=0_1136250_0_45572555&_dad=portal&_schema=PORTAL

3. Medical research funding in Europe and globally

non-oriented research and general university funds (GUF) as well as industrial production and technology for the pharmaceutical and medical devices industries. The Frascati Manual (2002, p.145) defines the SEO protection and improvement of human health as “research aimed at protecting, promoting and restoring human health broadly interpreted to include health aspects of nutrition and food hygiene. It ranges from preventive medicine, including all aspects of medical and surgical treatment, both for individuals and groups, and the provision of hospital and home care, to social medicine and paediatric and geriatric research”.

Figure 1 shows recent government funding data for a cross-section of the 11 European countries where data are available and the USA. The weighted average European share of health-related R&D budget appropriations in GDP is more than 50% below the corresponding share in the US, in spite of the much higher GDP per capita in the USA. However, to arrive at a valid comparison for all EU15 countries, we would need to include Italy, Belgium, Portugal and Luxembourg, four countries that have not reported all their health-related government budget appropriations for research funding.

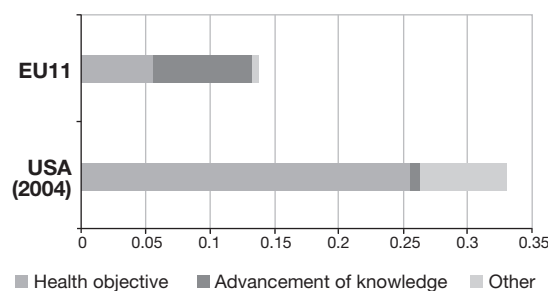


Figure 1: Government budget appropriations for health-related research, % of GDP

Note: The graph is based on the latest data and estimates for the years 2004 to 2007, depending on availability. Data are generally as reported by Eurostat for the health research objective, augmented by parts of budget appropriations for other socio-economic objectives that also contribute to health research. Where the latter are not available from Eurostat they have been supplied by Alison Young²³, from national publications and personal estimates. The category *advancement of knowledge* comprises primarily the part of general university funds that is used for medical research. But

²³ Alison Young, is a well-known international expert on science and technology indicators and independent consultant on health R&D to Statistics Canada and the Global Forum for Health Research, formerly with the OECD.

for France, the advancement of knowledge data covers all life sciences. The figures for the EU11 aggregate are GDP-weighted averages of the corresponding figures for the eleven EU members included in the graph. The health objective part of our data is in line with the structure of government R&D budgets that the European Commission's DG Research (2007) reports in 2007 in Table II.1.3²⁴ as being largely unchanged since 2000. For the USA, funding from all federal government departments, such as the Departments of Defense and Energy, the Environmental Protection Agency and the National Aeronautic and Space Administration and the Veterans' Administration, is included – although the vast majority of funding comes from the Department of Health and Human Services and is administered by the National Institutes of Health. Incidentally, so is federal spending for bio-defence research.

The use of sector of performance data allowed all EU15 countries to be analysed, and largely confirms the strong lead of the USA relative to Europe.

Figure 2 compares estimates of minimum health-related R&D performed in the non-market sectors in the EU15 countries and the USA during 2004 that have been provided by Alison Young²³. The dataset was compiled largely from the results of the joint OECD/Eurostat R&D questionnaire for 2004 using the methodology proposed in the Frascati Manual (2002). Where expenditures on medical research performed in the higher education, government and private non-profit sectors were not available, funder reports of R&D for the health objectives were used as a substitute. Where both were available, Alison Young selected the higher figure. The underlying definition of medical sciences involves numerous subfields in basic medicine, clinical medicine and general health sciences, but does not follow the 2007 revisions²⁵ in the Frascati Manual that recommend broadening the definition and including new fields, such as medical biotechnology. Overall differences in price levels between countries were taken into account by using European purchasing power parities.

The combined total minimum spending on medical R&D in the EU15 countries is only 67% of the minimum spending in the USA, as compiled by the OECD.

Other sources, published in the highly respected peer review journal *Journal of the American Medical Association (JAMA)*²⁶ have identified much higher spending levels for medical research in the USA. These differences arise partly because the minimum

²⁴ EC DG Research (2007). Key Figures 2007 on Science, Technology and Innovation – Towards a European Knowledge Area.

²⁵ OECD (2007). Revised Field of Science and Technology (FOS) Classification in the Frascati Manual. Paris: OECD.

²⁶ Moses, H., Dorsey ER, Matheson DHM and Thier SO. Financial Anatomy of Biomedical Research. *Journal of the American Medical Association* 2005; 294 (11):1333–1342.

3. Medical research funding in Europe and globally

performance estimates by the OECD cover only R&D in the medical sciences proper, excluding the health-related component of other life sciences and the social sciences. Much of the health research funded by federal government departments other than the Department of Health and Human Services is not reflected in the minimum performance estimates. If R&D performed in universities outside the medical sciences, in particular in biology, is included, this increases the USA total by over 20%. Another reason is that research funders traditionally report higher sums for a given year than do the performers, especially where the amounts are rising rapidly, as it takes time for the funds to move from commitment to final expenditure. Thus USA government appropriations for health-related R&D, underlying Figure 1, were about USD 33 billion, whereas estimated performer receipts from government were only about USD 25 billion.

Differences also occurred because there were no reliable data for health-related R&D financed by State and Local governments, and estimates can differ markedly. Research America²⁷ estimated that federal government funding and other funds flowing into the non-market sectors in 2004 exceeded USD 49 billion, or Euro 42 billion at purchasing power parity. Another calculation²⁷ – funded by the Alerion Institute and the Boston Consulting Group – put total USA funding for medical research performed in the non-market sectors at USD 40.1 billion in 2003, with USD 26.4 billion spent by the National Institutes of Health, USD 6.9 billion by other federal agencies, USD 4.3 billion by state and local governments and USD 2.5 billion by private non-profit sources.

Relative to GDP, the USA non-market sector spent between 0.25 and 0.43% in 2004 on biomedical R&D, compared with 0.17% for the EU15 countries in the same year. Since most European countries have much more centralised administrative structures to disburse public funding for medical R&D, and private institutions such as charities and private universities tend to play a smaller role, the standard errors of the European figures are likely to be much smaller than in the case of USA estimates.

The large lag in European biomedical research spending contrasts with a much smaller lag in

government spending for other socio-economic objectives and other fields of science. In 2004, OECD data imply a combined total government funding for *all* research and development in the EU15 at approximately 80% of the USA level.

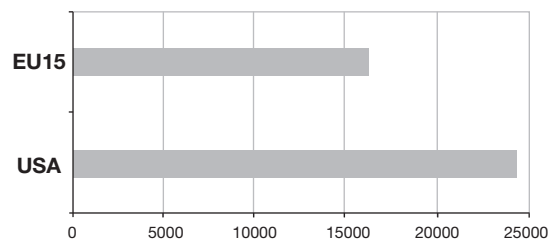


Figure 2: Minimum expenditures on health-related R&D performed in the non-market sectors 2004, in million Euros purchasing power parity

Note: The figure for the EU15 aggregate is the sum of the corresponding figures, using purchasing power standards, for the first fifteen countries to become EU members included in the graph. These data have been provided by Alison Young²⁸, mostly from the joint OECD/Eurostat R&D survey, except for Germany, France, the UK, Italy, the Netherlands and the USA. She used national publications and some estimates to arrive at a comprehensive picture. France and the Netherlands publish national tables on gross domestic expenditures on research and development at various times. Data for France are an estimated update from base 2001. Data for the USA have been updated using national publications from base 1997. For Italy, it is assumed that 25% of university R&D is in the medical sciences. For the UK, a funder-reported figure was used as a proxy since no suitable performer-reported data were available. Data for Germany were from an unpublished special analysis made by the Deutsche Forschungsgemeinschaft (2007) of the data from Germany's Federal Statistical Office that includes biomedical research in the fields of medicine, biology, pharmaceutical and nutrition sciences and excludes agricultural, forestry, horticultural and veterinary research, so that the reported data are equivalent with international definitions of biomedical research performed in the government and higher education sectors. The German data refer to year 2005, and so do the Swedish and Greek data.

Figure 3 plots per capita non-market sector spending on biomedical research against the share of “health” in all non-market research. This is not meant to imply causality, but to help distinguish the level of health research from the weight of health in the overall research portfolio. For the USA, the graph includes the strictly performer-reported figure from the OECD, which

²⁷ Connelly, E., and S. Propst (2005). 2004 Investment in U.S. Health Research – About 6¢ of health dollar is spent on research. Research America (5/2005). Retrieved from <http://www.researchamerica.org/publications/appropriations/healthdollar2004.pdf>

3. Medical research funding in Europe and globally

is equivalent to the minimum expenditures on health research in Figure 2, as well as the largely funder-reported figures reported in Connelly and Propst (2005) and Moses et al. (2005). It must be noted that the performer-reported figure that Connelly and Propst attribute to the USA higher education sector is likely to be an overestimate as they included all fields of science, not just the human health-related subset of university research. Moreover, the USA funder-reported figures for medical research outside the higher education sector are not strictly comparable with the performer-reported figures for *all* gross domestic expenditures on research in the non-market sectors that were used to calculate the percentage ratios on the horizontal axis.

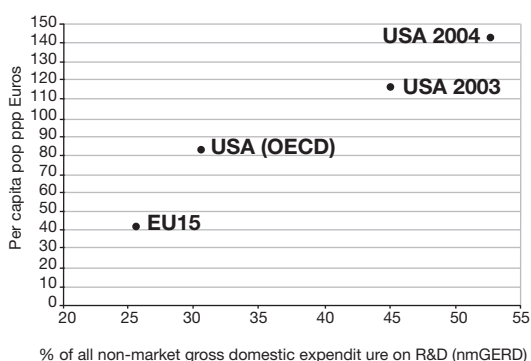


Figure 3: Performer-reported per-capita spending on biomedical research and the share of health in all research expenditures performed in the non-market sectors 2004

Note: USA (OECD) refers to the same data, compiled on the basis of the OECD/Eurostat R&D survey, that were used in Figure 2. Data for the USA in 2003 is taken from Moses et al. (2005)²⁸. Data for the USA in 2004 are from Connelly and Propst, *Research America* (5/2005)²⁹. Data for Germany refer to year 2005, as described in the legend to Figure 2, and so do the data for Sweden and Greece.

A more detailed comparison of components of health research spending in the USA market and non-market sectors reported by Moses et al. (2005) for 2003 and Connelly and Propst (2005) for 2004 is given in Figure 4 below. It appears that the differences in the aggregate

estimates arise mainly from different estimates for Federal Government agencies other than the NIH and from the university sector where the peer-reviewed JAMA article by Moses et al. (2005) provides no estimate.

	Connelly & Propst (2005)		Moses et al. (2005)	
Industry				
Pharma	39		27	
Biotechn	10	59 bn	18	54 bn
Medical Techn	10		9	
Federal Government				
NIH	28		26	
Other	10	38 bn	7	33 bn
Other				
University	7		NA	
State/Local	3	12 bn	4	7 bn
Foundation	2		3	
	109 bn		94 bn	

Figure 4: Comparison of USA Funding of Biomedical Research by Sources in 2004 (Connelly & Propst, 2005) and 2003 (Moses et al, 2005) (in USD Billion)

To highlight the distinct time trends in the European and USA non-market sectors over the past ten years, Figure 5 sets all spending on medical research 1995 equal to 100, and plots the observed growth in spending relative to that base level. The strong acceleration in USA federal spending on biomedical R&D during the years 1999 to 2003, as reported in Moses et al. (2005) has since begun to level off, and has even declined slightly, but the sector of performance data underlying Figure 5 has continued to show growth, as it typically lags source of funds data by one or two years and includes funding from sources other than the USA federal government. An important contributor have also been non-profit organizations. However, we note that adjusted for inflation, using the USA biomedical R&D price deflator that is calculated by the National Institutes of Health, the growth in USA spending

²⁸ Moses, H., Dorsey ER, Matheson DHM and Thier SO. Financial Anatomy of Biomedical Research. *Journal of the American Medical Association* 2005; 294(11):1333 – 1342.

²⁹ Connelly, E., and S. Propst (2005). 2004 Investment in U.S. Health Research – About 6¢ of health dollar is spent on research. *Research America* (5/2005). Retrieved from <http://www.researchamerica.org/publications/appropriations/healthdollar2004.pdf>

3. Medical research funding in Europe and globally

has been about one-third lower in real terms than in nominal terms over the 1995 to 2003 period, as reported in Moses et al. (2005).

USA developments contrast sharply with those in the world's second largest economy, Japan, where only 50% spending growth in nominal terms was observed between 1996 and 2005. However, in a period of general deflation, it is likely that a biomedical R&D price index for Japan would have shown more stability for most of the past ten years, perhaps even a decline in some of those years. Eurostat reports that Japan's total expenditure on biomedical research in the non-market sector accounted for only 17.9% of all research spending in that sector in 2003, up from 15.5% in 1996, and the ratio to total health-care spending was 1.8% in both years, virtually the same as the average for the EU15 countries. Relative to GDP, Japan's non-market biomedical research spending was at 0.13% in 1996 and 0.14% in 2004, about the same as the weighted average for the 11 European countries shown in Figure 1.

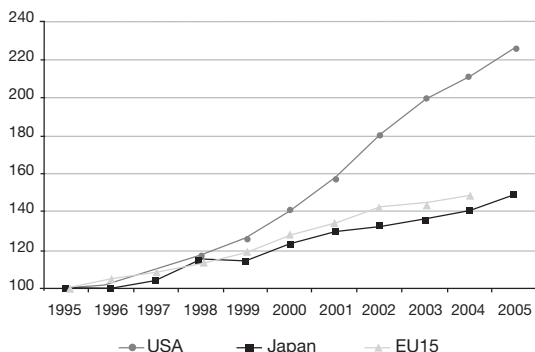


Figure 5: Time trends for nominal medical research expenditures performed in the non-market sectors, relative to 1995 levels (=100) in national currencies

Note: For Japan, Eurostat has not reported the 1995 value and we assumed the same level of expenditures as observed in 1996.

The EU15 countries as a group appear to have experienced slightly higher spending growth than Japan, with a nominal increase of biomedical research expenditures performed in Europe's non-market sectors at just below 50% from 1995 to 2004.

In conclusion, it is obviously difficult to achieve valid, robust and unquestionable data about the funding for medical research in Europe and in the USA. The EMRC recommends that data acquisition in the future should be correct and with up-to-date research definitions, and reported by all governments following the same "gold standard".

Yet no matter how the available data are analysed and compared, biomedical research funding in the USA is much larger than in Europe³⁰. Relative to GDP the USA non-market sector spent between 0.25 and 0.43% in 2004 on biomedical R&D (depending on the way university research is included and on the data source used), compared with 0.17% for the EU 15 countries the same year. The most credible estimate for the USA lies between 0.37 and 0.40% more than twice the European spending relative to GDP and almost three times the European spending when measure relative to the size of the population.

³⁰ The JAMA data were recommended to us from the NIH.



4. Medical research outputs in Europe and globally

Research output measured in publications and citations

Medical research aims at improving understanding of basic aspects of life, and ultimately prevention or cure of diseases. A single and simple link between biomedical research and major clinical breakthroughs is rare as most discoveries build on extensive background information. Moreover, new discoveries require a long validation and implementation process before they can lead to improvements in healthcare. Therefore direct measurement of medical research outputs is usually estimated on the basis of proxy criteria such as publications, patents (with real exploitation), and major awards such as Nobel and Nobel-like prizes, but such events usually recognise innovations and inventions that took place many years previously. Bibliometric analysis is normally regarded as the best method to estimate quality of research output, as the quality of the journal publishing the data and the subsequent citations to these publications are the earliest markers of respect or appreciation by peers. Such a system is of course subject to over- and underestimation before, at or shortly after the publication. Many examples can be cited, with hindsight, where there was unjustified attention and appreciation, or especially the lack of it, but such exceptions should not disqualify the use of bibliometric analysis for most cases.

To compare research output of the USA with that of the 15 original EU member states, raw bibliometric data were extracted from the 1996–2005 annual volumes of the Web of Science (WoS) of the Institute for Scientific Information (Thomson Scientific, Philadelphia, PA, USA). The extracted data have carefully been cleaned and then processed to give standard bibliographic indicators. All papers of the document type *articles, letters, notes and reviews* indexed in the 1996 and 2005 annual updates of the WoS have been included. Citations received by these papers have been determined for the three-year period beginning with the publication year on the basis of an item-by-item procedure using special identification-keys made up of bibliographic data elements. The last publication year that could be

taken into account for the citation analysis was therefore 2003 (citation window: 2003-2005). Papers were assigned to countries based on the corporate address given in the by-line of the publication. All countries indicated in the address field were thus included. An integer-counting scheme has been applied; each publication has been assigned as a full paper to all countries contributing to the paper³¹.

Publications

The number of publications indexed by the WoS database has increased every year. This is in line with the general growth of scientific literature. Both the number of covered journals and the number of papers published by most journals are continuously growing. The strong increase of USA and EU publication is therefore not surprising. In particular, the total number of publications with EU15 origin (between 1996 and 2005; about 1.32 million ISI publications) slightly exceeded the number of USA publications in the study period (1.25 million) with a 25% and 23% increase between 1996 and 2005, respectively. In order to obtain a realistic picture of the evolution of publication activity, figures should be normalised by the world total in the field under study. The share of EU15 and USA biomedical publications of all worldwide biomedical publication has remained fairly stable over the last 10 years (Figure 6). However, the “EU advantage” reached its peak around 2000; beyond this year the deviation between the EU and the USA contributions to the world output in this field began to shrink. This observation is in line with the general pattern in all science fields combined³². **The per-capita publication output of the USA exceeded that of the EU15 output by roughly one paper per 10,000 inhabitants.** In particular, the output per 10,000 inhabitants changed from 3.2 (1996) to 3.9 (2005) in Europe, compared to from 4.4 to 4.9 in the USA over the same period.

³¹ See Annex 1 for complementary information on the methodology used for this analysis.

³² Glänzel, W. Debackere, K. Meyer, M. 'Triad' or 'Tetrad'? On global changes in a dynamic world. *Scientometrics*, 2008;74 forthcoming

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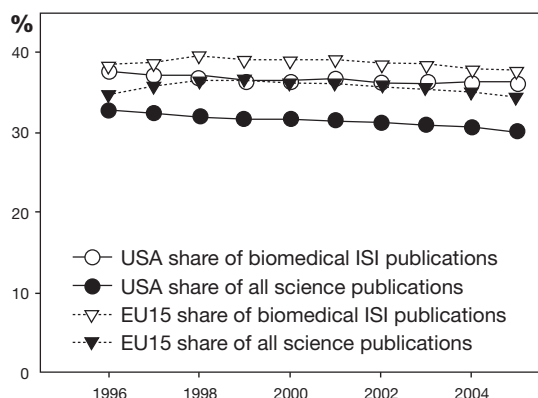


Figure 6: Share of EU15 and USA in total or biomedical ISI publications 1996-2005

Citations

The value of publications to the scientific community can be assessed in different ways, but on a macro scale citations to publications are a good marker for visibility and science impact, although some distortions may occur due to conscious or unconscious preferential unscientific citations of specific publications. However, US authors more frequently cite other US authors than authors outside the USA³³, and English language publications are favoured in citation databases³⁴. The total number of citations to US publications 1996–2003 largely exceeded the number of citations to EU15 publications during the same time period (Figure 8A), with a 40 and 56% growth respectively between citations to publications from 1996 versus 2003. The share of the world citations to biomedical publications remained about 50% and 40% for USA and EU15 publications, respectively (Figure 7B) throughout the studied period (1996–2003).

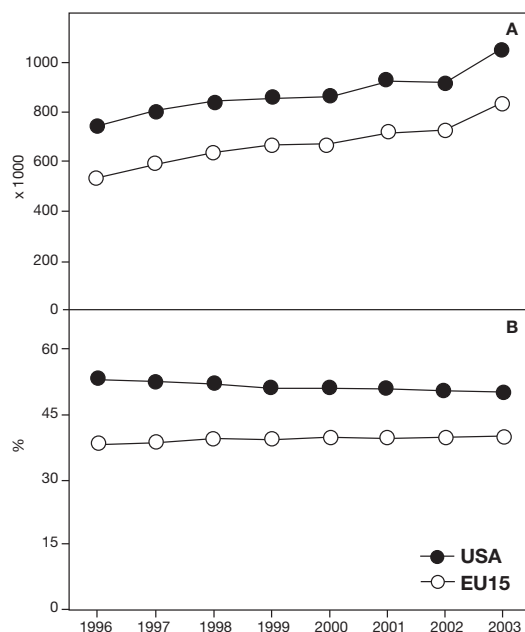


Figure 7: Biomedical research output from USA and EU15 estimated from ISI citations to publications from 1996 to 2003

A. Crude citation number

B. Share of EU15 and USA citations

(100% = citations to all worldwide biomedical publications)

It can be seen that the mean observed citation rate (MOCR) was always substantially higher for US than EU15 publications, with a steady difference of about two citations per publication. This relative difference remains important even when corrected for the journal standard (MECR, Figure 8A) and became even bigger when corrected for sub-field (NMCR, Figure 8B).

Both the journal-based relative citation rates of Europe and the USA are thus distinctly higher than the world standard where the US indicator-values even exceed those of the EU15. However, for the corresponding field-based indicators, the countries of the European Union have substantially lower citation rates than the USA; indicator values of around one for the EU reflect a citation impact just in line with the world standard, while those of the USA lie distinctly above this standard. The

³³ Glänzel, W. Schubert, A. Domesticity and internationality in co-authorship, references and citations. *Scientometrics*, 2005;65:323-342.

³⁴ Winkmann G, Slutius S, Schweim HG. Publication languages of impact factor journals and of medical bibliographic databank. *Deutschland Medizinische Forschungsrichte* 2002;127:131-37.

4. Medical research outputs in Europe and globally

ratio of the two indicators confirms that American scientists publish on average in journals with distinctly higher impact (factor) than their European colleagues, and this difference remained stable throughout the observation period.

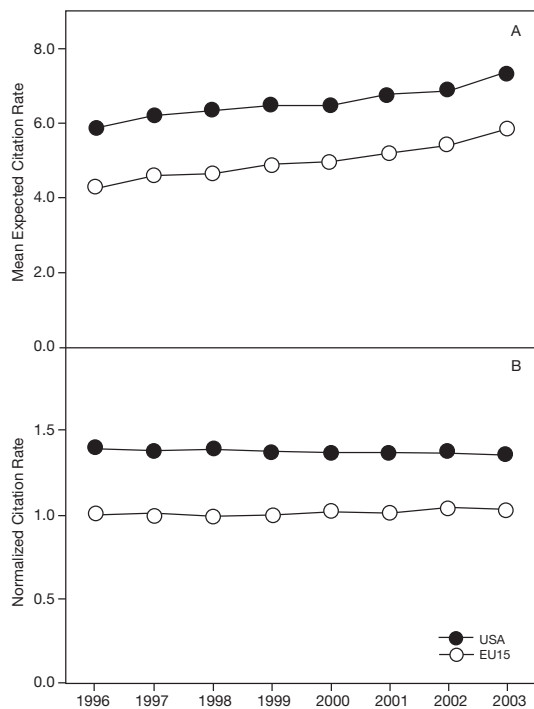


Figure 8: Biomedical research output from USA and EU15 countries estimated from citations from 1996 till 2003 publications

A. Mean expected citation rate = average citation rate of all papers [in the same journal in the same year] during the subsequent 3 years
B. Normalized citation rate = mean observed citation rate / weighted average of citation rate for the subfield

Of special interest for the specific case of biomedical research are data recently published by the National Science Foundation³⁵ – the world share of the top 1% and 10% cited articles by field on research in 2003 and shown in Figures 9 and 10 below.

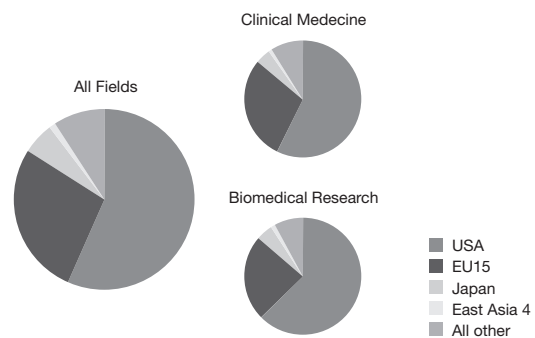


Figure 9: World share of top 1% cited articles by field (2003)

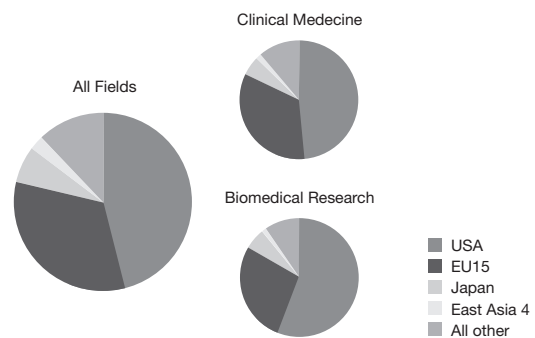


Figure 10: World share of top 10% cited articles by field (2003)

³⁵ Hill D, Rapoport AI, Lehming RF, Bell RK. Changing U.S. Output of Scientific Articles: 1998-2003. (2007) National Science Foundation, Division of Science Resources Statistics, Directorate for Social, Behavioral, and Economic Sciences.

4. Medical research outputs in Europe and globally

In conclusion, the bibliometric analysis of biomedical publications clearly demonstrates the dominant role of the USA and EU15 in biomedical research. As shown in Table 1, jointly they produced about two-thirds of the world total in this field³⁶. The EU15 countries published slightly more biomedical publications than the USA over

the last 10 years, but the number of citations the USA publications received far exceeded the number of citations to EU15 publications. This suggests a quality difference in research visibility, reception and impact of the published results, but may also partly be due to a positive English language bias in citation databases.

Table 1 Publication and citation indicators on biomedical research in the USA and Europe-15 (1996-2005)

Year	US/EU	Papers	% Papers	Cites	% Cites	MOCR	MECR	RCR	NMCR	NMCR/RCR	% SCIT
1996	USA	117764	37.7%	745519	53.2%	6.33	5.87	1.08	1.38	1.28	21.3%
	EU15	119674	38.3%	535322	38.2%	4.47	4.27	1.05	0.99	0.94	26.7%
1997	USA	119343	37.1%	801213	52.2%	6.71	6.19	1.08	1.38	1.27	20.3%
	EU15	124208	38.6%	591509	38.6%	4.76	4.58	1.04	0.99	0.95	25.3%
1998	USA	122660	36.8%	838425	51.9%	6.84	6.33	1.08	1.38	1.27	19.8%
	EU15	131541	39.5%	635559	39.4%	4.83	4.64	1.04	0.99	0.95	24.3%
1999	USA	123072	36.5%	860480	51.0%	6.99	6.46	1.08	1.37	1.26	19.5%
	EU15	131980	39.2%	668585	39.6%	5.07	4.89	1.04	1.00	0.97	23.3%
2000	USA	122375	36.4%	861225	50.9%	7.04	6.48	1.09	1.36	1.25	19.1%
	EU15	131196	39.1%	673718	39.8%	5.14	4.96	1.04	1.02	0.98	22.5%
2001	USA	124944	36.7%	924603	51.0%	7.40	6.78	1.09	1.36	1.25	19.0%
	EU15	133182	39.1%	720266	39.8%	5.41	5.21	1.04	1.01	0.98	22.1%
2002	USA	121892	36.2%	918449	50.6%	7.53	6.88	1.10	1.37	1.25	18.3%
	EU15	129599	38.5%	724462	39.9%	5.59	5.38	1.04	1.03	0.99	21.3%
2003	USA	131393	36.2%	1049874	50.1%	7.99	7.30	1.09	1.35	1.24	17.9%
	EU15	138913	38.3%	837218	39.9%	6.03	5.79	1.04	1.03	0.99	20.8%
2004	USA	127419	36.9%	:	:	:	:	:	:	:	:
	EU15	130769	37.9%	:	:	:	:	:	:	:	:
2005	USA	144034	36.2%	:	:	:	:	:	:	:	:
	EU15	149538	37.6%	:	:	:	:	:	:	:	:

³⁶ The figures in Table 1 due to EU-US collaboration are not additive, and may therefore not be summed up to the total.

5. European medical research needs to be strengthened

If the present level of funding for medical research in Europe were brought up to the US level, and if this were combined with enhanced European collaboration and implementation of “best practice”, this would create a very strong medical research base in Europe. It is important that Europe meets future challenges in the most intelligent and effective ways. We recommend a substantial increase in the funding of medical research from the European Commission, the European Research Council (ERC), from all the national funding agencies and charities, and from the European medical and pharmaceutical industries.

This should primarily be achieved by increasing the total expenditure for science and research, and only secondarily by shifting resources within the existing research budgets.

Implementation of “best practice” in how to spend research money is necessary; this is described in detail in Chapter 6, “How to improve medical research in Europe”. We propose a set of tools on how to spread “best practice”, with a focus on collaboration and distribution of funding after peer review, and the use of excellence criteria. Other mechanisms include improved career track schemes and mobility, more focus on equal opportunities (including gender), and more focus on interdisciplinary research – where Europe should take the lead. A strengthening of research infrastructure is necessary for basic, translational and clinical medical research, as proposed in the European Strategy Forum on Research Infrastructures (ESFRI) Roadmap³⁷. Enhanced collaboration between academia and industry through private–public partnerships will also be important, an example being the new EC Joint Technology Initiative, the “Innovative Medicines Initiative”⁶¹.

Europe is progressing in the right direction. The EC Framework Programme 7 (FP7), with a larger budget than ever for research, is starting this year. The new ERC represents an important and positive

step towards excellence for European research. The budget for the ERC is about a quarter of the total FP7 budget, and thus about 2% of the total research budget in Europe. (FP7 distributes about 8% of the total public research budget in Europe, with 12% of FP7 allocated for medical research).

The ERC has rightly placed a strong emphasis on bottom-up applications and funding distribution on the basis of excellence; this is crucial for the whole field of medical research. These principles should be used by all national and international funding bodies, covering all areas of medical research – from basic research, through translational to clinical research and public health and epidemiology. The ERC will hopefully set standards for the future development of European research practice. As Ernest Starling advised the British Research Council in the 1920s: “*Get the best of men, give them the equipment you can afford, and leave them alone*”³⁸. (In those days very few women were doing medical research – it is improving).

The National Institutes of Health (NIH) in the USA, have for 2007 an annual budget of USD 28.4 billion³⁹, one common strategy and a globally-acknowledged peer review system with emphasis on bottom-up research and excellence. The US shares one language for research publications, and there is an acknowledged set of values for research funding, evaluation and performance. We have many different languages in Europe, and we need to overcome fragmentation, different approaches to peer review and excellence criteria, and heterogeneity of economic welfare, research infrastructure and of healthcare systems.

The number of European publications in the field of medicine is comparable to that of the USA, but their citations are fewer. Part of this observation may be due to the citation effect – Americans quote Americans^{40,41,42,43,44,45}. There is an English language bias in citation and impact-factor derivations⁴⁶; the overall share of English language publications in the citation databases is around 90%.

³⁷ The European Roadmap on Research Infrastructure (Report 2006) http://ftp.cordis.europa.eu/pub/esfri/docs/esfri-roadmap-report-26092006_en.pdf

³⁸ Ernest Henry Starling (1866 – 1927) Physician and Physiologist – A short biography by Jens H. Hendriksen. Lægeforeningens forlag, Copenhagen (2000).

³⁹ AAAS August R&D Funding Update: ‘Congress endorses competitiveness increases, adds funds for biomedical, environmental, and energy R&D in 2008’ AAAS – August 6, 2007 – Page 1-8.

⁴⁰ Nylenna M, Riis P, Karlsson Y. Multiple blinded reviews of the same two manuscripts, effects of referee characteristics and publication language. *JAMA* 1994 Jul 13; 272(2):149-151.

⁴¹ Callahan M, Wears RL, Weber E. Journal prestige, publication bias, and other characteristics associated with citation of published studies in peer-reviewed journals. *JAMA* 2002;287:2847-2850.

⁴² Campbell FM. National bias: a comparison of citation practices by health professionals. *Bull Med Libr. Assoc.* 1990;78(4):376-382.

⁴³ Link AM. US and non-US submissions: an analysis of reviewer bias. *JAMA* 1998;280(3):246-247.

⁴⁴ Grange RI. National bias in citations in urology journals: parochialism or availability? *BJU International* 1999;84:601-603.

⁴⁵ Ross JS et al. Effect of blinded peer review on abstract acceptance. *JAMA* 2006;295:1675-1680.

⁴⁶ Winkmann G, Slutius S, Schweim HG. Publication languages of impact factor journals and of medical bibliographic databank. *Deutschland Medizinische Forschungsrichte* 2002;127:131-37.

5. European medical research needs to be strengthened

Biomedical research and innovation systems in the EU and in US regions differ in many ways as presented in Annex 2 and summarised in Table 2 below.

Table 2: Comparison of the biomedical research and innovation systems in the USA and in the ERA⁴⁷

	USA	ERA
Research Infrastructure	Decentralised universities. Multidisciplinarity and extensive collaboration among the various parties already routinely embedded and represent an asset in moving biomedical research from discovery to commercial development and developing integrative ('bench to bedside' and vice versa) and relational capacity (PPP).	Centralised with hierarchical control and mainly public universities. Single field orientation and need for multi-sites collaboration to integrate all competencies required to develop new medicines. Reliance on adequate scientific programming to create the adequate environment for translational research.
People	More research independence and mobility of faculty members at early career stage. High salaries for scientists (x3 EU) Incentives to increase the physician-scientists population. Promotion of entrepreneurship early in the education system.	Limited autonomy and mobility for younger researchers. Low salaries. Limited examples of initiatives to increase the physician-scientists population.
Funding	Diverse sources (public/private): I) Substantial public R&D funds administered through the NIH (28.4 billion USD 2007) supports basic (60%) and translational & clinical (40%) research and allocated through a stringent peer review based on excellence; II) Alternative and complementary sources.	National and European public sources: I) Nationally-dispersed funding (<i>data not available</i>); II) EC funding by DG Research for cooperation in Health priority (Euro 6.1 billion for the period 2007-2013).
Regional idiosyncrasy	US has a science and result oriented culture. Large positive balance between the number of collaborative R&D projects originated and developed.	Europe is characterised by an administrative and management culture. Divide between the developers of ideas and those who originated them.
Innovation	Unique patenting system. Federal mandate e.g., Bayh-Dole Act (1980).	European Patent still under discussion. Creation of intermediary institutions for technology transfer introducing an additional layer between university and industry.

⁴⁷ Riccaboni, M., Powell, W.W., Pammolli, F. and Owen-Smith, J. (2004). Public research and industrial innovations: a comparison of U.S. and European innovation systems in the life sciences. In A. Geuna, A. Salter and E. Steinmueller (Eds.). Science and Innovation: Rethinking the Rationales for Funding and Governance. Cheltenham, United Kingdom: Edward Elgar Pub., (Chapter 10)

5. European medical research needs to be strengthened

Several USA research institutions and universities are ranked very highly in worldwide comparisons⁴⁸. There is a large number of European Universities (> 2000), but only a few have a biomedical research output which is able to compete with the best US universities. There is a need for strengthening the best research universities in Europe, so that they may reach critical mass in terms of excellence and documented research output, as is proposed in the EC Green Paper. Academic medical centres (university and research hospitals and equivalent healthcare centres) carrying out tertiary medical care, teaching and clinical research produce a large part of the biomedical research in Europe. They are subject to a continuing demand for improved efficiency and cost-effectiveness in patient care, and this may restrict their ability to undertake medical research. The academic centres and university hospitals are important research infrastructures, and are the “real world” laboratory equivalent for clinical research, comparable to the laboratories essential for basic science. It is important to ensure excellent conditions for clinical research throughout Europe in these university hospitals and academic medical centres.

Europe needs to be prepared for the rapidly changing disease patterns that are emerging with increased globalisation and climate change, including new serious diseases. Collaboration between major centres and extensive long-term funding of biomedical and clinical programmes is more important than ever. For major endeavours, both in the basic and clinical sciences, large-scale funding and long-term planning and support are needed, together with collaboration and coordination. A new strategy is needed leading towards strong and well-funded European medical research, for better health, welfare and economy in Europe. The consequences of improved funding for medical research in Europe will help to fulfil the recommendations of the EC Green Paper.

⁴⁸ See the 2007 Academic Ranking of World Universities at <http://ed.sjtu.edu.cn/ranking.htm>



6. How to improve medical research in Europe

In some European countries medical research has developed positively over the last decades, while in other countries medical research is facing more difficult conditions⁴⁹. We recommend that improved funding for medical research should be combined with tools for implementing “best practice” in the future. We suggest that these tools should be implemented quickly and widely to ensure that the quality and output of future medical research will be maximised. This will benefit the European society, its patients, citizens, and the European medical industries.

Primary goals

Strong basic biomedical science, with strong clinical research and translational research that takes innovative ideas into clinical practice is very important – with proof-of-concept studies, including clinical, pathophysiology, experimental medicine, phase I, followed by phase II and III trials. We should share both methodology and results across Europe and the rest of the world. Research conferences, learned societies and scientific journals have a crucial role, together with the EC and the national private and public organisations. The European Congress and Society of Radiology with their European Institute for Biomedical Imaging Research – EIBIR⁵⁰ is a good example of how this translational research can be organised. The recommended pathway consists of evaluation of the research results by meta-analyses, Cochrane reviews, clinical guidelines and Health Technology Assessments based on the principles of evidence-based medicine. It is important that we implement research results into better patient treatment employing such evidence-based principles. Translational research, which is a very important focus area for medical research at present, is bi-directional in its nature, with sharing and transfer of ideas and inspiration from basic research to clinical research and *vice versa*, and indeed may sometimes be even more complex.

Interdisciplinary research is more important now than ever, between medical fields, and between medicine, engineering, the natural and physical sciences, technology, mathematics, molecular biology, the humanities and social sciences. The medical programme at the European Synchrotron Radiation Facility (ESRF) in Grenoble (France) is an excellent example of such a fruitful collaboration. Niels Bohr often advocated interdisciplinary collaboration between natural sciences and medicine; himself, together with George de Hevesy, being the founding father of nuclear medicine. There has been an increasing number of successful examples of interdisciplinary research over recent years with the teams behind MRI scanners, new radiation therapy for cancer drug development, modern genetics. It is both in the interdisciplinary areas, and in the more focused research areas, that new important knowledge will be achieved in the future. In Europe we have a strong tradition and capability in physiology, pathophysiology and experimental medicine, and in the eastern European countries there are particular strengths in the natural sciences, including among physicians.

Public–private partnerships can make valuable contributions to medical research in Europe. In the public domain we could learn from industry: their principles for running research and development laboratories, their strategies and leadership. Industry knows how to change strategy very fast; we should listen and learn from them. An example is the LEAN⁵¹ principle, where the Toyota factory invented a new quality procedure for doing all procedures with the fewest achievable steps. Recognition of research undertaken in the private medical research sector should be better recognised and used by universities and academic institutions, and the European medical industries should know which are the best research teams and infrastructures, and should be encouraged to develop strategic alliances to help transfer knowledge to discovery and commercial development.

⁴⁹ Gluud C, Nikolova D. Likely country of origin in publications on randomised controlled trials and controlled clinical trials during the last 60 years. *Trials* 2007;8: 7.
<http://www.trialsjournal.com/content/8/1/7>

⁵⁰ More at: <http://www.eibir.org/cms/website.php>

⁵¹ <http://www.mep.org/textfiles/LeanPrinciples.pdf>

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Tools to reach these goals: people

Training and career track schemes with attractive possibilities for researchers in biomedical research are very important. The competitiveness of Europe in biomedical science is totally dependent on its capacity to train, recruit and retain a large and customised pool of scientists, engineers and physicians. To be attractive to researchers, Europe has to develop a favourable research environment where excellence, visibility, transparency, security, flexibility and diversity are the driving forces.

In this context, promoting training and new career track profiles should take into consideration the following:

i) Specific measures to reinforce **training** of medical doctors (MDs) in science, and training of scientists in medicine or more clinical disciplines, to enhance the continuum from basic to translational and clinical research and *vice versa*. Universities, and in particular university hospitals, will play a major role in combining high-level training programmes and world-class research centres. The postgraduate education of MDs is a very important area, where a future “EMRC, Forward Look” report should be considered. The setting-up of more MD/PhD programmes across Europe, with the degrees obtained in parallel, should be the goal. The universities and hospitals (both in Europe and elsewhere) which already have successful programmes, should be used as models.

ii) Well-defined **recruitment policies** to establish a balance between short-term and tenured or longer-term career positions, with more visibility and **career prospects**, are needed. An important step has been achieved with the recent EC adoption and dissemination of a European Charter for Researchers and of a Code of Conduct for the Recruitment of Researchers⁵². A small number of countries, including France and Italy, consider senior scientists as civil servants, while others have favoured career track positions based mainly on renewal of research contracts. Whatever the case, clear high-level temporary contracts for

young researchers with a recognised social status, either at university or within research-performing organisations (RPOs), should be part of a defined career track that gives real prospects to brilliant young researchers.

Such contracts, of at least five years, awarded according to stringent scientific assessment, could be followed by access to a tenure-track and/or a permanent position, depending on the laws in the different member states.

In order to fulfil one of the main objectives of the FP7 – to promote translational research and innovation – there is a need to create incentives to scientists to transfer knowledge and competencies, as well as to support multi-disciplinary research. Initiatives are being introduced in Europe to supplement the remuneration of career researchers with a “top-up” provided by the partner institution through a temporary contract, flexible in its duration. This new scheme aims to provide stability during the career of the researcher and encouraging medium- to long-term research, while at the same time fostering more risky and short-term approaches dedicated to knowledge transfer and translational research.

At the European and International levels, similar initiatives in different countries could help define a real “European career for researchers”, and provide strong incentives, both financial and in terms of career development.

For Europe to be fully competitive and productive in research, it is imperative that men and women have equal opportunities to develop and use their full intellectual capacity.

This means that men and women must have equal opportunities to compete for research funds, to play their part in scientific decision-making and to find gainful employment in publicly-funded research.

Equal opportunity exists when two criteria are fulfilled. Firstly, formal equal opportunities must prevail. This is achieved when everyone is subject to the same legal framework and rules when pursuing a career or achieving a goal. Secondly, those with similar abilities and the

⁵² http://ec.europa.eu/eracareers/pdf/am509774CEE_EN_E4.pdf

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same willingness to use them should have the same prospects of success.

In general, men and women possess the same inherent ability and willingness to perform research of high quality. However, in Europe as a whole, women form only a minority of leaders in publicly-funded research, are under-represented in scientific decision-making, and have a lower success-rate when applying for research funds⁵³. These disparities are largely a consequence of social differences; and these vary both within and between cultures, are learned, may change over time.

Redressing the gender balance in science is consequently a matter of research policy, and gender equality in science has been high on political agenda in the last 20 years. Strategies to raise awareness of gender bias and to increase the number of women in academia, especially in leading positions, have been introduced with varying success. It is important that the effects of these different measures are closely monitored, evaluated and developed in order to ensure equal opportunities between men and women in science.

iii) Incentives for encouraging geographic as well as inter-sector **mobility** of researchers during their professional lives. Mobility is a global issue, important not only within Europe. The EC should be congratulated for actions such as the European Researcher's Mobility Portal, but consideration should now be given to a European Visa. Furthermore, the development, or convergence, of the social security and tax systems across Europe in to promote mobility is a major challenge. Such mobility should be viewed positively as a criterion for promotion and career advancement.

It is essential that there is no scientific fraud, and that we adhere to the highest ethical standards in biomedical research. In Europe, we share common values concerning honesty, humanity, altruism and democracy. Such issues are themselves subject to academic study, and must be supported by the whole European medical research area and engrained in all who conduct research, from students and young researchers

to the most senior researchers and administrators in universities, research establishments and hospitals.

Tools to reach these goals: research infrastructure

New large research infrastructures are necessary for the development of medical research in Europe, from national investments in basic science laboratories and hospital facilities for research to larger national facilities, and to large pan-European infrastructures, as proposed in the ESFRI Roadmap 2006, which has six proposals in the field of biomedical research. The university hospitals and academic medical centres in Europe are responsible for approximately 50% of medical research⁵⁴, and they are therefore important research infrastructures in medicine. New large collaborative research infrastructures in basic research, translational research, clinical applied research including good manufacturing practice (GMP) facilities are important, as well as biobanks and registries that enable basic, translational, clinical and public health research. Here the EC can help European medical research substantially by supporting the relevant ESFRI proposals. The new paradigm of personalised medicine based on the human genome and molecular analyses of tumour markers and of metabolism will be a challenge, and should be supported and further developed to deliver better patient treatment.

A better, more intelligent and coordinated use of Information Technology (IT) including telemedicine, are important tools for research, as well as for the implementation of research results into patient care. IT will be as important for future biology and medical research as mathematics was for physics research in the 20th century⁵⁵. The value to research of electronic patient records, biobanks and registries is dependent on the intelligent use of IT. There is a need to initiate a debate with the public about the use of patient data (from research and healthcare) for the benefit of the wider European population.

⁵³ She figures 2006 - Women and Science Statistics and Indicators http://ec.europa.eu/research/science-society/pdf/she_figures_2006_en.pdf

⁵⁴ Gluud C, Nikolova D. Likely country of origin in publications on randomised controlled trials and controlled clinical trials during the last 60 years. *Trials* 2007,8: 7. <http://www.trialsjournal.com/content/8/1/7>

⁵⁵ Microsoft Research Report (2006) Science 2020 <http://research.microsoft.com/towards2020science/downloads.htm>

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EC and national regulations need to be reviewed to facilitate collaboration across countries. The disincentives arising from the growing number and complexity of directives, laws and regulations need to be alleviated. This is especially important for multi-centre trials involving several countries, which are difficult to carry out. Rules and regulations are necessary to secure patient safety and integrity and to protect researchers, but they must be designed to meet the new challenges, including the need to exchange information from data registries, electronic patient records and biobanks between countries. It is very important that the rules and regulations foster research. At present, the rules and regulations can be serious barriers for clinical studies, inter-disciplinary studies, especially those involving many partners. Here the EC can help medical research substantially by providing an impact assessment of those directives that may impact on medical research (even if this is not their primary aim), with the goal of ensuring safety for patients, while at the same time making it easy for researchers to collaborate in research aimed ultimately to deliver new treatments to patients. Although there is already some work in this area in the EU, this needs to be developed substantially. (For details see Annex 3).

Tools to reach these goals: research funding

Adequate funding is the “*sine qua non*” for medical research. The use of peer review to distribute research funding on the basis of on scientific excellence remains the best way to support high-quality research cost-effectively. Since the 1950s peer review has been the mechanism for distributing limited research funds, and for centuries it has served as the main selection mechanism for the publication of scientific articles. In short, peer review involves an assessment of a research proposal or research outcomes by researchers (“peers”) who have the necessary knowledge and experience to be able to judge the proposal or manuscript submitted. It is part of a competitive process aimed to identify good research and to prevent poor or duplicative research from taking place. The use of peer review

by research funding agencies is complicated as the assessment is directed towards the **potential** of research, rather than simply to assess previous research findings. To evaluate research before it has actually been done is, of course, risky. This means that the track-record of the applicant is also of great importance in the process.

Peer review is a fundamental and critical part of the research process, as it serves as the main mechanism for judging the merits of research, and subsequently the best way to advance knowledge and serve the public interest. This means that there is immense pressure on the peer review system to differentiate between excellent, good and poor research. For peer review to function properly, certain prerequisites are necessary. To begin with, in order to make the judgement, assessors should not be in a position to benefit personally from the process (conflict of interest). Furthermore, it is also essential that the process operates in a transparent fashion that ensures a fair and trusted outcome.

A peer review procedure cannot entirely remove all biases or totally escape an element of luck, as the process is not capable of making fine-tuned distinctions about quality – especially between proposals in different areas. It is inescapable that a system of human decision-making is liable to fallibility. It is important to continue to recognise the imperfections of peer review, and try to minimise them to make the process as effective as possible. In essence, there remains no viable alternative to the use of peer review to assess research quality. Peer review can be implemented in various ways. Furthermore, it is by no means a static enterprise – it is itself under constant review. Among funding agencies efforts are being made to improve the efficiency and transparency of the peer review process without compromising key principles⁵⁶. There is co-operation between funding agencies, including the exchange of practices and ideas, and it is important that this should continue in order to refine the process. The overall conclusion is that an effective form of peer review is vital to sustain public confidence in the scientific community through the support of high-quality research.

⁵⁶ An example can be found at : www.rcuk.ac.uk/news/eepr.htm

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Medical research funding distributed according to excellence criteria and judged by peer review is at present the best way to ensure that the best applications get funded.

A balance between “bottom-up” and “top-down” research approaches is necessary; the former being more researcher-driven and the latter more strategic. Basic biomedical research published in journals such as *Nature*, *Cell* and the *EMBO Journal* have higher citations (and thereby higher impact scores) compared to clinical research papers, for example in surgery, published in clinical journals. This is partly due to different research and publication traditions⁵⁷, but may also reflect that the criteria for ‘originality’ intrinsically differ between such areas. However, medical research in the field of surgery is necessary for health and wellbeing, and relevance criteria in this field are therefore as important as originality. Thus medical research is needed in all areas. Research in each area should be measured by its own criteria for excellence, with comparisons made within similar research areas; i.e., surgery compared with surgery, and basic science with basic science. It is important that peer review does not discriminate against certain groups such as young researchers, females. In Europe the percentage of research funding distributed following peer review involving at least one international reviewer is not known. The FP7 budget is 7–8% of the total R&D public funding in Europe, and funding through ERC is 2% of the total. Both programmes apply international peer review. In European countries peer review is often used by private charities and medical research councils, and the use of international peer review is known to vary, though many national medical research councils and charities use international peer review for larger applications. The EMRC recommends that international peer review is used more widely. It will increase transparency and fairness, and secure a real competition on the basis of excellence.

The effective use of peer review will speed up change from aristocracy to meritocracy.

There should be equal opportunities in all aspects of medical research, independent of a researcher’s age, gender, origin, profession, race, religion or sexual orientation.

A common approach to the evaluation of the research outcomes

The outcome of research grants can be assessed and evaluated in a number of different ways and with different purposes, as described above. The national research councils follow up the results of the research they have supported at varying intervals, employing a number of different methods. This is done for internal management reasons and for reporting back to governments and the tax-payer. In both cases the information may be used to help formulate future research needs and strategies. Private foundations and charities have similar obligations to report back to their sources of funding. However they are free to decide whether, and to what extent, they undertake follow-up analyses of the outcome of the research they fund. Presently, there is no single source of information about how, and to what extent, private and public research funders evaluate the impact of the research they fund. The Lundbeck Foundation (DK) has initiated collaboration with the Wellcome Trust (UK) on the development of a common methodology for the evaluation of research grants in Europe. A similar initiative in the USA, the Health Research Alliance⁵⁸, which fosters collaboration among non-for-profit, non-governmental funders to support the continuum of health research and training, has established working groups on programme evaluation, grant administration and outreach to funders. A common approach to the evaluation of the output and outcome of research grants should be developed and implemented, for both privately and publicly funded grants. This will provide information to assist funders of research to use their resources in the most effective way.

⁵⁷ Seglen PO. Why the impact factor of journals should not be used for evaluating research. *BMJ* 1997;314:498-502.

⁵⁸ More at: <http://www.healthra.org/groups.html>

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Tools to reach these goals: societal means

Collaboration, sharing of research results and partnerships between research areas, disciplines, institutions, countries and between academia and industry, as suggested in the EC Green Paper (2007), are essential in order to improve research in Europe. An open, helpful and transparent approach is needed between all those in the ERA, where we acknowledge the differences in history, culture and traditions between countries, research areas and disciplines. Some countries have been underprivileged, with very limited means for research through the last century, and there has been a substantial gap between East and West Europe – as well as between Europe and the developing world. Science is global, and a culture that strengthens collaboration and sharing of results will benefit not only science and society in Europe, but also science globally – and help medical research bloom. Globalisation, including collaboration across Europe from East to West and between Europe and the rest of the world, with the US and the rapidly-growing economies of China, India, Singapore, South Korea, Brazil and Russia, is essential in the field of medical research. We should not aim for a future locally self-sufficient European Research Area, but for an ERA with strong research groups working in collaboration with other strong research groups, wherever they may be and of whatever discipline, as suggested in the EC Green Paper, where sharing knowledge and opening to the world are regarded as essential. One centre or one country may not be able to complete the largest and most complicated R&D project alone, and therefore international collaboration is needed to cope with increasing research complexity. An open access publishing policy is especially important in cases where the best R&D results are needed fast for the whole world, as is the case for new serious and rapidly emerging infectious diseases.

The need has been expressed to gain more information about the programmes in Europe and in USA where we do have open access and where we do have reciprocity. An open system with reciprocity should be carefully designed and requires further discussion.

In the European medical research area, we should focus on collaboration and on how to share competencies between East and West, North and South in a mutually respectful way, based on equity and listening to each other's experiences and needs for the future. Those who have been privileged with good conditions for R&D, with well-equipped infrastructure and well-equipped hospitals, and those who have been deprived of research funding for a long time, but who have competencies and capacities, should collaborate and share across Europe, so that we can reach the same high level within a foreseeable future. The key features are openness, transparency, trust, mutual recognition, respect and sharing of scientific knowledge and know-how.

We should listen and learn from each other, and ensure the efficient dissemination of knowledge. It is important that the results of research are implemented quickly into patient care. To address differences observed in the current status of biomedical research in Eastern and Western countries in Europe (as presented in Annex 4) the following recommendations are made.

There should be a concerted effort to raise public awareness of the impact of medical research on health and welfare. The Eurobarometer 2004 on entrepreneurial attitudes in Europe and the USA⁵⁹ has shown that public awareness has previously been higher in Europe. It is part of a person's general education to be taught how the body functions, why diseases emerge and how diseases can be prevented. Such knowledge can increase the implementation of research results from public health and preventive medicine and produce major beneficial effects for society. Increased public awareness of the benefits of medical research and its challenges will make research of general interest to the people of Europe.

Preparedness is essential for the future development of Europe. As described in the introduction, we are a changing society within a global environment, with newly emerging infectious diseases, bioterrorism and changing disease patterns. Tuberculosis is increasing in

⁵⁹ EOS Gallup Europe Flash Eurobarometer 160 "Entrepreneurship" (2004): http://ec.europa.eu/enterprise/policy/survey/eurobarometer_survey2004.htm

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Europe, with new and rapidly changing microbial resistance. Rapid and dramatic climate changes predicted in the future will modify the disease patterns and present a major challenge. A changed demography with an ageing population in Europe will increase demand for healthcare. An epidemic of obesity and metabolic syndrome will be another substantial challenge for Europe, with diabetes and its related side-effects. The post-modern global society with increased societal stress, fear of the future, together with a changing European demography, will provide major challenges in mental-health-related diseases.

In conclusion, medical research is vital if society is to successfully meet many of its future challenges. Increased funding of medical research will yield a high return for society, leading to better and more cost-effective healthcare systems, a healthier population, better quality of life, and an expanding economy for European medical industries. Expenditure on healthcare in Europe has been growing rapidly, whereas investments in medical research have been more modest.

Strengthening Eastern Europe medical research

- Develop private funds and charities.
- Stronger repatriation funds to help reverse brain drain.
- Develop the private sector, with focus on entrepreneurship and innovation.
- Increase numbers of PhD and post-doctoral fellowships.
- Establish regional networks of scientific excellence and graduate schools.
- Expand economic clusters in biomedicine into Eastern Europe.
- Develop national research strategies for the knowledge-based societies of tomorrow.

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Tool Box: “Best Practice” for medical research in Europe:

Primary goals:

- Strong basic research
- Strong clinical research
- Strong translational research: bringing basic research knowledge into clinical practice, and *vice versa*
-- all three of the above being facilitated by interdisciplinary research and public-private partnerships

Tools to reach these goals: people

- Career track schemes with attractive possibilities for researchers taking advantage of co-funding strategy
- European Medical Scientific Training Programme (EMSTP) for physicians and scientists scaling up existing successful initiatives
- The highest level of research ethics, and no scientific misconduct

Tools to reach these goals: research infrastructure

- Investment in national and European research infrastructure – covering the whole range from laboratory equipment in basic science labs and research facilities in hospitals, to the largest pan-European infrastructures, as outlined in the ESFRI Roadmap
- Launch a call for proposals to directly support on a highly competitive basis a league of top performing biomedical research centres of excellence, integrated into regional clusters
- Post-genomic clinical medicine
- Intelligent and coordinated use of Information Technology (IT)
- EC and national regulatory issues for clinical research adapted to facilitate research

Tools to reach these goals: research funding

- Adequate research funding – distributed on the basis of scientific excellence and through peer review
- Common criteria and methods for the evaluation of research outcomes

Tools to reach these goals: societal means

- Globalisation and collaboration: sharing of research and results
- Public engagement about medical research and its possible impacts
- Preparedness for the future

7. Scenarios for the future development of medical research in Europe

If we improve funding for medical research in Europe with a doubling of public funding within the next 10 years to a minimum level of 0.25 % of GDP for each country, and combine this with implementation of “best practice” for optimum collaboration and organisation of medical research in Europe, there will be major benefits for European society, including better health, welfare, hospital treatment and a thriving medical industry. The documented large returns on investments in medical research support such an intervention.

Investment in medical research will result in a substantial increase in new patents and peer review publications. However, more importantly, new European-based discoveries and innovations in genomics, molecular biology, studies of brain function, mental health, tumour biology, immunology, vaccines and pathophysiology will lead to new and improved treatments. The discoveries will provide better diagnosis, treatment, rehabilitation and prevention. They will also lead to a substantial growth of Europe’s medical industry.

The creation of an active and positive medical research environment in Europe will lead to a virtuous circle, with more investment from industry, including the return of some of the investments that European companies are presently making in the USA, in areas such as pharmaceuticals, biotechnology, devices and medical technology. There will be a marked impact on society in terms of a better economy. The result of introducing evidence-based medical treatment in European hospitals will be significant, with both cheaper and better healthcare. For example, the research that led to “fast track surgery” reduced the average in-patient-days for a number of surgical procedures⁶⁰. The return on the research investment behind this was many hundred-fold if costs are counted per procedure.

If we do not improve the conditions for medical research in Europe, European medical research will be impeded, with serious consequences for society. Bearing in mind the well-known aphorism: “*If you think research is expensive; try disease*” (Mary Lasker, 1901–94), one should note that expenditure on medical research is only a small proportion of total expenditure on healthcare and hospitals, and if we do not use research to control

the healthcare costs of tomorrow, the economic consequences will be serious.

The gulf in quality between medical research in the USA and in Europe will increase, and the newly emerging BRIC⁶¹ economies will increasingly represent another challenge. A cycle will develop with serious negative effects for European medical industries and hence for our economic welfare. The negative impact on patients, human welfare and our economy caused by old-fashioned, expensive and outdated hospital systems will be pronounced. The newly emerging diseases, the ageing population and the epidemic of diabetes and obesity will, together with societal changes in demography and anticipated climate changes, result in a society heavily dependent on good healthcare and welfare.

We should focus on the positive aspects of medical research. New research areas such as the “-omics” and systems biology, nanomedicine, regenerative medicine, tissue and stem cell banking should be encouraged, with collaboration and open and international access by scientists and industry. Significant advances in new methodologies including nanotechnology, the “-omics”, molecular genetics with deciphering of the role of non-coding regions of genome in disease development will improve clinical medicine resulting, ultimately, in pre-symptomatic diagnostics. Preventive medicine, together with individually tailored therapy and personalised medicine will be an important outcome of basic and applied medical research. This should also shorten the length of time it takes to discover and bring to the market new drugs.

Creating a sizeable common pot by pooling resources at the European level for activities such as large-scale clinical trials or advanced translational research will be an important achievement. We should regain society’s trust by educating the public about the benefits of medical research, and we should increase awareness of evidence-based medicine, and the inappropriate utilisation of alternative/complementary medicine. Greater harmonisation and interlinking of clinical trials and their results across Europe should be promoted in order to facilitate cross-border studies and evaluation of all kinds of therapy.

⁶⁰ Kehlet H, Dahl JB. Anaesthesia, surgery and challenges in postoperative recovery. *Lancet* 2003;362:1921-28

⁶¹ BRIC : Brazil, Russia, India, China

7. Scenarios for the future development of medical research in Europe

Disparate national regulations governing stem cell research in Europe prevent the field from benefiting from the internationality of approach inherent to scientific advance⁶² (EMBO). The current stance of the European Patent Office is to exclude from patentability all inventions or claims relating to human embryonic stem cells. Rule 23d(c) of the European Patent Convention stipulates that “European patents may not be granted with respect to biotechnological inventions which, in particular, concern uses of human embryos for industrial or commercial purposes”. This situation puts the European biotech sector at a disadvantage compared to the USA and other non-European countries active in the field. This issue should be solved in Europe, not only for the benefit of European medical research, but, more importantly, for the benefit of Europeans.

The EMRC has an important role in the future development of medical research in Europe through its science policy and foresight activities, such as the recently published Forward Look on “Nanomedicine”, and the launch of a new Forward Look on “Investigator Driven Clinical Trials”. Through the active participation of our member organisations and in dialogue with the European Commission, the European Research Council and others, we can share ideas, facilitate their implementation, and enhance collaboration in the medical ERA. Together we can bring European medical research from the present second position to be the global leader. It is not our aim to strive for a position as number one merely for the sake of winning a competition. The real issue is to ensure future prospects for health and welfare. In the next ten years we need to secure a doubling of funding for medical research in Europe by increasing the total expenditure for research, and to implement “best practice” for organising medical research and development – this for the future benefit of all Europeans and for the rest of the world.

⁶² Kraljevic S., Stambrook P.J., Pavelic K.: Accelerating drug discovery. *EMBO Rep.* 2004; 5: 837-842.
Stem Cell Research. Status, Prospects, Prerequisites. EMBO, Heidelberg, 2006.

8. Recommendations for strengthening medical research in Europe

1. Implementation of “best practice” for funding and performing medical research (see tool box).
2. Collaboration via EMRC and its Membership Organisations and EC, ERC, COST, the scientific societies, the medical journals and the university and academic medical centres to enhance collaboration and sharing of research and results.
3. Revision of EC Directives related to medical research to facilitate research.
4. Endorsement of the EMRC statement on equal opportunities for performing research: “The EMRC advocates equal opportunities in all aspects of medical research – regardless of age, gender, origin, profession, race, religion, or sexual orientation.”
5. A doubling of public funding of medical research in Europe within the next 10 years – to a minimum level of 0.25 % of GDP and the necessity for sustaining a steady growth above inflation in the years to come after the doubling.



Annexes

Annex 1: Medical research outputs in Europe and globally (Chapter 4)

Subject classification of publications was based on the field assignment of journals (in which the publications in question appeared) according to the twelve major fields of science and three fields of social sciences and humanities developed in Leuven and Budapest (see *Glänzel and Schubert, 2003*). Details are given in the following section.

• The structure of the field as reflected by the Web of Science data base

BIOSCIENCES (GENERAL, CELLULAR & SUBCELLULAR BIOLOGY; GENETICS)

- B0 multidisciplinary biology
- B1 biochemistry/biophysics/molecular biology
- B2 cell biology
- B3 genetics & developmental biology

BIOMEDICAL RESEARCH

- R1 anatomy & pathology
- R2 biomaterials & bioengineering
- R3 experimental/laboratory medicine
- R4 pharmacology & toxicology
- R5 physiology

CLINICAL AND EXPERIMENTAL MEDICINE I (GENERAL & INTERNAL MEDICINE)

- I1 cardiovascular & respiratory medicine
- I2 endocrinology & metabolism
- I3 general & internal medicine
- I4 hematology & oncology
- I5 immunology

CLINICAL AND EXPERIMENTAL MEDICINE II (NON-INTERNAL MEDICINE SPECIALTIES)

- M1 age & gender related medicine
- M2 dentistry
- M3 dermatology/urogenital system
- M4 ophthalmology/otolaryngology
- M5 paramedicine
- M6 psychiatry & neurology
- M7 radiology & nuclear medicine
- M8 rheumatology/orthopedics
- M9 surgery

• Methods and Results

In order to shed light on the evolution, impact and competitiveness of European biomedical research, the following publication measures and citation-based indicators were used.

- i) Publication count, that is, the number of papers published by the unit under study. For the European Union, duplicates caused by intra-European collaboration have been removed.
- ii) Share of publication output in the world total.
- iii) Citation count, that is, the number of citations received within a three-year citation window beginning with the publication year.
- iv) Share of citations in the world total based on three-year citation windows.
- v) Mean Observed Citation Rate (MOCR). MOCR is defined as the ratio of citation count to publication count. It reflects the factual citation impact of a country, region, institution, research group etc. A three-year citation window has been applied.
- vi) Mean Expected Citation Rate (MECR). The expected citation rate of a single paper is defined as the average citation rate of all papers published in the same journal in the same year. Instead of the one-year citation window to publications of the two preceding years as used in the Journal Citation Report (JCR), a three-year citation window to one source year is used, as explained above. For a set of papers assigned to a given country, region or institution in a given field or subfield, the indicator is the average of the individual expected citation rates over the whole set.
- vii) Relative Citation Rate (RCR). RCR is defined as the ratio of the Citation Rate per Publication to the Expected Citation Rate per Publication, that is, $RCR = MOCR/MECR$. This indicator measures whether the publications of a country or institution attract more or less citations than expected on the basis of the impact measures, i.e., the average citation rates of the journals in which they appeared. Since the citation rates

of the papers are gauged against the standards set by the specific journals, it is largely insensitive to the big differences between the citation practices of the different science fields and subfields. It should be stressed that in this study, a 3-year citation window to one source year is used for the calculation of both the numerator and denominator of RCR. $RCR = 0$ corresponds to uncitedness, $RCR < 1$ means lower-than-average, $RCR > 1$ higher-than-average citation rate, $RCR = 1$ if the set of papers in question attracts just the number of citations expected on the basis of the average citation rate of the publishing journals. RCR has been introduced by *Schubert et al.* (1983), and largely been applied to comparative macro and meso studies since. It should be mentioned that a version of this relative measure, namely, CPP/JCSm is used at CWTS in Leiden (see *Moed et al.*, 1995).

viii) Normalised Mean Citation Rate (NMCR). NMCR is defined analogously to the RCR as the ratio of the Mean Observed Citation Rate to the weighted average of the mean citation rates of subfields. This indicator is a second expected citation rate; in contrast to the RCR, NMCR gauges citation rates of the papers against the standards set by the specific subfields. Its neutral value is 1 and $NMCR > (<) 1$ indicates higher(lower)-than-average citation rate than expected on the basis of the average citation rate of the subfield. NMCR has been introduced by *Braun and Glänzel* (1990) in the context of national publication strategy. A similar measure (CPP/FCSm) is used at CWTS (cf. *Moed et al.*, 1995).

ix) The ratio $NMCR/RCR$ reflects the average level of journals chosen for publication. In particular, $NMCR/RCR > 1$ (< 1) means that the journal impact of periodicals where the unit publishes is on average higher (lower) than the subject impact where the unit is active.

x) Share of author self-citations (%SCIT) is used as an auxiliary indicator.

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Annex 2: Biomedical research systems in the EU and US regions differ (Chapter 5)

• Research Infrastructure

The US research system, having become established as the main driver in biomedicine, is now reaping the benefit of setting up the best practice and methodologies, resulting in the EU becoming a follower, although at the national level some member states are also within the leader group. Unlike the US decentralised system that promotes a synergistic effect of diverse sources of funding even for public universities (Riccaboni et al., 2004), the EU has established a strict and centralised administration of research which has had the effect of reducing the flexibility and efficacy necessary for competitive research (Chu, 2004; Riccaboni et al., 2004). This might differ at the national level in Europe. The USA has generated clusters of centres of excellence around public organisations, integrating innovation and development work. These clusters attract talented researchers and highly qualified students, planting the seeds for increasing shares in research and development as well as attracting for-profit firms dedicated to the commercialisation of new technologies. When compared with the USA, the EU shows less capacity for the commercial exploitation of its basic research findings. The US institutions have more protocols on research collaboration with different organisations, and they actively serve as a link between basic research and clinical and industrial developments (Riccaboni et al., 2004). Part of these capabilities comes from the solid investment made in infrastructure and the strong funding for basic research. The latter also increases other outcomes, such as publications and patents. It is interesting to note that US companies not only dominate the patenting process in the USA, but they also take out more European patents than do European companies themselves (LERU). A general overview suggests that the EU needs to establish a better research culture in private industry, commerce, and the public healthcare system. One of the current barriers to an effective interface between industry and universities is the ownership of intellectual property rights (LERU). For some companies, Europe also seems to be less attractive place for investment than the USA because of the relatively low spending on overall healthcare (Sheridan, 2006).

• People

In order to achieve the best biomedical science, the best biomedical researchers are needed. There is a general agreement that in both the EU and the USA, the physician-scientist population is smaller and older than it was 25 years ago. In order to address this concern, certain programmes have been designed to recruit physician-scientists. Between 1998 and 2002, several initiatives were promoted in the US by the National Institutes of Health (NIH) and private foundations, including loan payment programmes, grants for starters, programmes to interest medical students in research, etc. (Ley and Rosenberg, 2005). Five years later, Europe started similar programmes to attract scientists in general and physicians in particular. For example, in 2003, the Academic Medicine Committee of the Royal College of Physicians in England established a Forum on Academic Medicine to discuss and to propose solutions for attracting students into research in general and for each of the different clinical specialties (Pusey and Thakker, 2004). The US programmes were accompanied by financial support, and it has been shown recently that as a consequence the number of physician-scientists is increasing. Due to the delay and to a more theoretical approach, any benefits of the European programmes have not yet been assessed.

Currently, the salary of a scientist in the USA may be three times that in the EU for the same position. Lower salaries in the EU are one of the main reasons why some of the brightest European scientists continue their careers in the USA after their postdoctoral training (Chu, 2004). Only 13% of European science professionals working abroad declare an intention to return home.

European scientists - especially the younger ones - present less autonomy and mobility than those in the USA for finding better positions in appropriate research institutions (Riccaboni et al., 2004). A lack of mobility can impede the creation of the right research groups at the right place, where they could generate new ideas and procedures.

Different indicators sustain the view that the EU offers scientists - especially younger ones - fewer opportunities than does the US to develop a successful scientific career. Young European

scientists have to work for many years before starting an independent group. To attract the best physician-scientists, the proper tripartite combination of elements that sustain academic medicine - teaching, research, and clinical practice - has to be ensured (Sheridan, 2006).

A further marked difference between Europe and US is the less pronounced European eager to patent own scientific achievements, and to develop new, small biotech companies and collaborate with the industry. Europeans generally exhibit a less pronounced “entrepreneurship” compared to Americans. Europeans prefer employee status while Americans opt for self-employed status⁷⁵. A more profound cultural difference may be the reason for this difference. However, Europe would benefit from more focus on innovation and private public-partnership in the field of medical research.

• Funding

European biomedical research is under-financed, and several specialties have raised concern about cuts in funding clinical research in particular. In recent years, funding in clinical research in the EU15 was 1.99% of GDP, compared with 2.76% in the USA (Sheridan, 2006). Investment has also shifted towards non-clinical research; for example, in Sweden, the number of grants for non-clinical research has risen by 50%, in contrast with a one-quarter drop in grants for clinical research.

Only Finland and Sweden have reached the EU target, agreed in Lisbon in 2000, of spending 3% of GDP on research and development (Chu, 2004; Soteriades and Falagas, 2005). The other EU countries clearly invest insufficiently in R&D, and for the whole Union to hit the proposed target by 2010, it should increase investment by some 8% a year, which is nearly twice the 4.5% annual increase recorded since 1997. The R&D investment in the EU by both government and industry is lower than in the USA in relative terms, and much lower in absolute terms. There are also fewer researchers in the workforce, and proportionally fewer PhD graduates in the industry (LERU).

In the EU, funding has tended to be administered centrally, with widely differing approaches across European countries. Moreover, European-wide programmes are much less likely than US ones

to support integration between science and clinical development. In the USA, institutions such as the NIH support significant interaction between the producers of fundamental biological knowledge and those involved in clinical research and technological development in public research centres and universities (Riccaboni et al., 2004).

• Regional idiosyncrasy

A major argument for understanding European difficulties in increasing the visibility of the output of its scientists could be the variability of the region as a whole, and even more importantly the specific characteristics of each country. Although there are few quantitative data to demonstrate this point, some qualitative information is available.

With regard to research and development, Europe is characterised by an administrative and management culture rather than a scientific culture. Moreover, the culture of competitiveness is modest, at least in some countries. In the EU, innovation and hard work are not always clearly rewarded with grants, full credit, and a financial stake in the work (Chu, 2004). A ethos of meritocracy is almost absent in many European countries, whereas there is a strong bureaucracy, rigid hierarchy, and a frustrating fragmentation of science.

In Europe, there is a divide between the developers of ideas and those who originated them. Research companies in large EU countries show a marked predilection to act as developers of R&D projects originated abroad (Riccaboni et al., 2004). By contrast, in the USA - followed by a group of small Nordic countries (such as Sweden and Denmark), Canada, and Israel - there is a large positive balance between the number of collaborative R&D projects originated and developed.

Taken as a whole, Europe could be a big enough biomedical research area to compete with other strong scientific markets. However, too often national interests overlap more general requirements. It seems that competitive funding has to be increased at the European rather than national level to encourage scientists to compete for EU grants, rather than taking what currently may be the easier route to apply for funding through their national programmes.

In Europe there is a poor public perception of science compared with in the US (Sheridan, 2006). Research findings need to be communicated to large audiences in a way that makes the achievements and limitations plain. Improved dissemination of science to the general public could result in an increase in financial support from individual donations and could lead to increased pressure on politicians to invest in research and development.

Taking together some of the arguments mentioned above, we conclude that in Europe biomedical sciences are developed less professionally and competitively than in the USA, and institutional stimulation does not seem to be a definite priority. This situation could lead those in the USA to the conclusion that both the impact and the penetration of a scientific article are stronger when associated with authors from a US laboratory. Even in Europe, often greater weight is attached to research carried out in the USA just for that reason.

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Annex 3: Regulatory landscape for clinical research in Europe (Chapter 6)

Current regulatory and legal framework for clinical trials in Europe

The current references in Europe for medicinal drug on human use are the following:

- First in place at the international level (US, EU, JP) ICH E6 for Good Clinical Practice (GCP) (1996)
- EU Directives: 2001/20/EC (and guidelines) enforced by 1 May 2004 and transposed into national law, completed by 2005/28/EC
- 2003/94/EC for Good Manufacturing Practice (GMP)
- EU Directive for medical devices 93/42/EC
- EU Directive for personal data 95/46/EC
- EU Regulation for paediatrics and rare diseases

There are other guidelines including draft for specific cases and new situations:

- Draft guidance on 'specific modalities' for Non-Commercial Clinical Trials referred to in Commission Directive 2005/28/EC laying down the principles detailed guidelines for Good Clinical Practice
- Draft guideline on requirement for first-in-man clinical trials for potential high risk medicinal products (EMA/CHMP/SWP/28367/2007): including chemical and biological medicinal products. It covers the first administration of a single dose of high-risk medicinal product and the initial single ascending dose phase of clinical development

Limitations

The European Union started life as a European Economic Community (EEC), prior to becoming a European Research Area (ERA). For this historical reason, the regulatory and legal guidelines for clinical trials in Europe were produced by DG Enterprise (as opposed to Ministry of Health or its equivalent at the Member State level), in order to address the economic imperative of the pharmaceutical sector to bring innovation to the European market. An important consequence of this situation was that when the EU Directive 2001/20/EC (and associated guidelines) for good clinical practice in relation to

investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, were written, non-commercial sponsors, such as medical research councils, national institutes of health, universities and clinical research networks, were not heavily involved.

Current EU legislation in this area focuses on the product (and is restricted to clinical trials on medicinal products), whereas the legal framework drawn up in individual Member States is also motivated by research and public health issues (and covers all categories of clinical research).

Recently, the EC DG Enterprise and the European Medicines Agency (EMA), were made aware of the limitations faced by researchers when implementing this EU Directive, in particular by the 'non-commercial sponsors'. The issues were raised at a conference on the operation of the clinical trials directive and perspectives for the future on 3 October 2007.

The 'non-commercial sponsors' represented by EMRC (the European Medical Research Councils), ECRIN (European Clinical Research Infrastructure Network) and others conveyed a number of important messages, including the following:

- the regulatory requirements should be based on the risk linked to the clinical trial and on the extent of knowledge on the product, not on commercial or non-commercial objectives.
- the scope of the legislation should be enlarged to all clinical research on humans including, for example, cohorts for genetic epidemiology, physiology and pathophysiology, proof-of-concept studies, treatment optimization, post-marketing surveillance, surgery, diagnostics, and so forth.

The report resulting from the conference is to be published on the EMA website in due course and was not available for inclusion in this White Paper.

What is needed?

We propose that EC and national regulations related to medical research should be made as simple as possible so that they facilitate and do not impede research.

Annex 4: Differences between Eastern and Western countries in Europe (Chapter 6)

The financial support to science in Eastern Europe is around 1 % of GDP, and with GDP per capita approximately half of the value of GDP in Western Europe; this creates a fourfold difference in favour of the Western countries. (This is probably a modest estimate of the difference, but no exact values are available, and it might be up to 6–8 times). Unlike for Western Europe the majority of research money in the East stems from state budgets. There are large differences between the countries within Eastern Europe, but it is obvious that Eastern Europe lacks research funding from the private sector, and Eastern Europe lacks private funds and charities supporting science.

In Western Europe pharmaceutical companies play a significant role in the advancement of science. The pharmaceutical sector in Eastern Europe still focuses on generic drugs, and the sector's R&D portfolio is marginal compared to the companies in the West. There is a gap in the development of biotech companies between East and West Europe, and the same is true about patenting of scientific discoveries. Unfortunately, it is not a common practice in Eastern Europe for scientists to think about commercialising the results of their work. Steps should be taken to improve this situation.

There is an obvious brain drain from West Europe to USA, and from East to West Europe. Repatriation funds should be developed in East Europe to return highly educated young scientists from the USA and West Europe. More government money should be spent on this issue. (To date, the Wellcome Trust and the Howard Hughes Fund have probably done more than the governments of East Europe). The instrument of post-doctoral fellowships attracting young scientists from other countries to work in the East Europe is also weakly developed. The number of PhD students in East Europe is lower than in West Europe. At the moment, the supply of PhD candidates is insufficient to meet academic needs for teaching medical students at an international level. There is also an insufficient supply of PhD candidates for clinical medicine, as well as of MD/

PhD candidates, and not enough scientists to support the needs of the private companies.

If the threshold for funding is the same across Europe, it may have negative impact, as they are fewer scientists in the East than in the West who will be able to meet the highest level at present. However, it is recommended that the PhD theses in medicine are based on international “peer-review” publications, to fight local “in-breeding” in biomedical sciences and to make the international scientific community share the responsibility.

The European Union provides significant help via structural funds in upgrading research facilities in East Europe. However, in the mid- to long-term this is not going to be sustainable if the governments of East Europe cannot find the money to properly maintain this newly developed research infrastructure.

East Europe should merge into the “common biomedical market” of Europe through:

- interaction with neighbouring countries belonging to the «Core group» of the EU;
- the development of regional networks of scientific excellence and graduate schools involving the countries of East Europe, and countries outside the EU, but located in the region; and
- the expansion of existing economic clusters in biomedical business into the countries of East Europe.

The development of a knowledge-based and science-driven economy should be a top priority for the governments of East Europe and to this end these countries should develop a clear action plan with a well-defined research strategy. The European Union has taken the first steps, now it is time for the East European countries to take the process forward.

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