MEDICAL DEVICES

COMPETITIVENESS

AND IMPACT ON

PUBLIC HEALTH EXPENDITURE

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EXECUTIVE SUMMARY

The medical device industry sector encompasses an extremely large variety of products and technologies. It covers hundreds of thousands of products that range from more traditional products, such as bandages or syringes, to sophisticated devices that incorporate bioinformatics, nanotechnology and engineered cells. These are designed for use by practitioners, patients and healthy individuals in a variety of settings: hospitals, surgeries and private homes.

Besides being a vital and innovative industry, medical devices are a key component of healthcare systems and represent, together with pharmaceuticals, the bulk of "medical technology". The analysis of the sector must therefore investigate medical devices as an industry – an innovative contributor to the economy – as well its key input to healthcare systems.

This Study provides an analytical overview of the state of the European Union medical device industry with regard to the following aspects: a) the impact of innovation in medical devices on health costs and expenditure; b) the innovativeness of the European medical device industry; c) the competitiveness of the European medical device industry as compared to that of the United States and Japan.

The worldwide medical device market in 2003 is valued at over €184 billion, with an estimated nominal increase of about 16 percent from the previous year. The US constitutes the largest world market for medical devices, representing a world share of 38-43 percent. The European market, at 30-34 percent of the world share, is the second largest market; here the two main national markets, namely Germany and France, account for half of its size.

Medical devices are a key component and provide a key input to health systems. In Europe, 6.2 percent of total health expenditure goes on medical devices. This percentage is higher for new Member States (7.6 percent) than for the EU-15 aggregate (5.4 percent). As compared to Europe, the share of medical devices over total health expenditure is lower both in the US and in Japan (about 5.1 percent).

Medical devices are also an important part of the European manufacturing sector. Despite growing pressures from national cost-containment policies that have curbed the positive trend of growth of the sector, the industry is extremely vital, driven by growing income, aging populations and in general societies' commitment to improving the quality of life. The industry – that contributes to at least 1.1 percent of total EU-25 manufacturing value added and to 1.3 percent of total EU-25 manufacturing employment – has shown a dynamic performance also during the recent years of economic slowdown. In 2001 and 2002 (the most recent year available) medical device production in the EU-25 has recorded strong growth rates (12.5 percent in 2001 and 7.8 percent in 2002), well above the average of the manufacturing sector (1.8 percent and 0.3 percent). The bright outlook for the sector is confirmed by its positive performance on the stock market, where medical devices have systematically outperformed the average market trend.

However, it is important to immediately point out that, in this vital and strategic sector of the economy, European industry is lagging behind the US, both in terms of competitiveness and innovativeness (see the summary statistics in Table 1).

On the international scene, data on trade in medical devices shows that the position of the US is more competitive than that of European countries, and especially Japan. However the US trade balance has decreased in recent years, while the position of European countries has not changed substantially over time. Moreover, the analysis at the sub-market level reveals the existence of high heterogeneity across sub-sectors and shows the "vocation" of the EU as a producer (and net-exporter) of electro-diagnostic equipment, a segment where the EU maintains a leading position.

Interesting differences emerge from the analysis of the industry structure. The European industry is characterised by a larger share of small firms than the US and Japan. In particular the average size of European medical device firms turns out to be smaller than the European total manufacturing sector, while the reverse is true for the US. In addition, US firms are more diversified than their European counterparts, even though high heterogeneity exists across European countries. This evidence has relevant implications in terms of access to resources and funding for research activities.

Indeed, when comparing R&D intensity of the European and US firms, the R&D intensity of US firms is much higher than the European level, the latter being roughly comparable to Japan.

In addition, the US plays a pivotal role as a supplier of technologies, as highlighted by the analysis of the international market for medical technologies. Again, it is important to notice that the medical device industry is extremely diversified and European countries turn out to be net exporters of technologies related to implantable devices, and, with respect to the US, of therapeutic equipment and supplies.

The leading role of the US in medical technologies is confirmed by the analysis of scientific productivity. The US has a leading position in terms of patent and publication counts, and more importantly, the gap with European countries widens when we consider the number of citations received by patents and the impact factor of publications.

Finally, the composition of US production highlights a larger share of high-risk devices commercialised by US corporations.

As compared to the pharmaceutical and biotechnology sectors, the medical device innovation system is characterised by smaller innovative firms, higher levels of interdisciplinarity and lower levels of cumulativeness of the knowledge basis.

The continuous flow of innovation in medical devices and related medical practices revealed in this Study through a number of case studies and statistical analyses, shows that medical devices are able to detect diseases earlier and offer more effective treatment options for leading causes of disability and mortality. Innovation in medical technology and devices appears correlated to the trend of improved health outcomes recorded for most countries in the world where patients are able to live longer, be healthier, and where they can be productive for longer over their lifespan.

The pressure on public budgets from accelerated healthcare spending that has affected most countries, in particular in recent years of economic slowdown, has opened the floor to new debate on the economic and financial impact – besides the medical one - of technological progress in medicine. Economic theory and models provide mixed indications on the medical technology–health expenditure link: the effect of cost-reducing technologies, increasingly stimulated by constrained health insurers, could in principle offset the cost-increasing interaction between growing health insurance schemes and technological innovations. It is then necessary to switch to empirical analysis in order to collect empirical evidence on these dynamics, and on the significance of the link.

The review of the increasing number of applied studies shows that although single new technologies may exert both upward and downward pressures on health costs and spending, new medical technology is believed to have generated expenditure increases in the aggregate. It is important to point out that the focus of the analysis here is on the cost of technological change, which is rising health expenditure. The side of the benefits of medical technology improvements – longer life, improved quality of life, prolonged working ability and so on – is not considered in this literature. As a consequence, no conclusions can be drawn here on the issue of the net value that patients and society in general derive from innovations.

Innovation in medical technology and devices is thus normally associated with rising healthcare expenditure. Despite their proved benefits, are innovations in medical devices and medicine then financially sustainable? What kind of policy measures should be enacted to sustain these improvements without constraining the number of beneficiaries and the acquisition and access to significant technologies?

The Study shows that the best way to approach these issues is to frame them into the broader debate on welfare system reforms that EU Member States will need to adopt over the next few years. In particular the Study is in line with a vast body of literature that suggests a mix of coordinated policies, often referred to as "triple diversification of the expenditure": I) a rebalancing within the components of public social expenditure, at present too concentrated on pensions; II) a rebalancing between public and private sources of financing through the adoption of co-payment schemes; III) a rebalancing within the composition of private social expenditure, in order to strengthen the organised institutional pillars of pension and healthcare funds. EU Member States appear to have margins to strengthen the diversification of the financing sources for the long-term sustainability of healthcare expenditures. With the appropriate use of market regulation, fiscal incentives and support to the disadvantaged categories of patients, this structural change can take place preserving the fundamental social choices. This could partially loosen budget constraints on health systems as well as the focus on cost-containment, and allow more room for high price-performance products both in the public and private markets. The industry of medical devices and of high-tech medicine could become one of the investment targets for health funds, and benefit from a significant financial source for R&D and innovation.

The provision of health insurance – public and private – has been key to innovation in medical technology and devices. The expansion of healthcare insurance in all national systems has nourished innovation in medical technology; and vice versa new technologies and new medical capabilities have expanded demand for insurance i.e. insurance that includes more people and encompasses more health procedures and products. Theoretical and empirical analysis shows that the diffusion of a number of existing technologies has been highly responsive to insurance-related incentives. In the past, the incentives injected in the market favoured the development of sophisticated medical technologies, regardless of their costs. The change in the incentives, marked by the move to prospective-based insurance systems, altered the direction of medical innovation towards the development of efficiency-enhancing and cost-reducing medical devices and practices. Measures that affect the incentives to innovation, such as reimbursement regulations, have proved to be policy tools for cost-conscious health insurers, capable of directing R&D incentives and innovation towards cost-reducing/quality-enhancing trajectories. Member States should enhance their coordination with the objective of engaging in coordinated policies, in order to send consistent signals to the market, reduce uncertainty, orient R&D and innovation toward cost-reducing technologies.

In order to turn this powerful mechanism into an effective policy option, it is necessary that:
1. these incentives are operated through reference criteria for "efficiency-enhancing" that can be addressed through technology assessment tools;
2. a harmonised system of data collection and diffusion is implemented and maintained among different institutions and Member States.

As far as the first point is concerned, it is useful to notice that despite the fact that the number of well-designed clinical trials have grown dramatically in the past years, and that medical journals now routinely publish cost-effectiveness analysis, the use of health technology assessment (HTA) by policymakers as an explicit part of the decisions on coverage, funding and clinical guidance, though increasing, is still limited, and confined to a minority of Member States. The process of implementation of HTA is at present progressing, with Member States adopting different methodologies and standards. Exchangeability and access to the evidence-based information for

policy-making and practice obtained through HTA would instead be enhanced by the harmonisation of the methodologies and standards of data compilation. The processes and initiatives in place, as for instance the ECHTA/ECAHI project, have so far led to partial results. On the one hand, Members States should enhance the use of evidence-based medicine and health technology assessment analysis as explicit parts of the coverage process for new medical devices. On the other hand, The Commission should reinvigorate this process of harmonisation and coordination through the enhancement and sponsorship of an effective and well-endorsed "European Network for Medical Technology Assessment".

Given the complexity and high level of heterogeneity of the medical device industry, a wide variety of data and information sources need to be combined to monitor the performance and role of the industry, at a national and international level. Given the severe shortage of reliable and harmonised data at the EU and international level, the conclusion of this Study should be carefully interpreted. The present lack of reliable and disaggregated data prevents the empirical assessment of the link between industry structural characteristics and international competition dynamics on the one side, and the level of competitiveness and innovativeness on the other. A major effort should be set forth to devise and develop a statistical framework for the analysis of the medical device sector, from the R&D and innovation stage to the market stage. Throughout this Study we have proposed ways to improve the quality of the data for the sector in order to sustain robust statistical analysis and evidence-based policy implications. As a first step, it would be very useful, within the revision of the NACE classification due out in 2007, to consider more disaggregated classes allowing the identification of relevant medical device segments. In addition, it would be extremely important to complete and make accessable the European Database on Medical Devices (EUDAMED).

Table 1. Summary statistics

	Year	US	Europe	EU-15	EU-25
Market (% World)					
Pharmaceutical Market	2002	46.5	25	21.6	
Medical Devices, Eucomed	2002	43	30		
Medical Devices, Datamonitor	2002	38	34		
Production					
Pharmaceutical (US$ millions)	2001	130,012		126,908	130,712
Medical Devices (constant 1995 € millions)	2001	55,002		31,059	32,139
Pharmaceutical (ratio w.r.t. US)	2001	1.00		0.98	1.01
Medical Devices (ratio w.r.t. US)	2001	1.00		0.56	0.58
Trade balance (export/import ratio)					
Pharmaceutical	2001	0.78		2.42	
Medical Devices	2001	1.46		1.15	
Value added over employees					
Pharmaceuticals (US$ thousands in 1997-PPP)	2001	319.6		193.2	
Pharmaceuticals (1995 € thousands)	2000	239.5		93,0	
Medical Devices (1995 € thousands)	2001	106.6		40.5	
Pharmaceuticals (PPP; ratio w.r.t. US)	2001	1.00		0.60	
Pharmaceuticals (x-rate; ratio w.r.t. US)	2001	1.00		0.39	
Medical Devices (ratio w.r.t. US)	2001	1.00		0.38	
R&D expenditures					
Pharmaceutical (R&D/production)	2000	10.96		10.91	
Medical Devices (R&D/Sales)	1999 US 2000-2002 EU	12.9		6.35	
Pharmaceutical (ratio w.r.t. US)	2001	1.00		0.99	
Medical Devices (ratio w.r.t. US)	2001	1.00		0.49	

	Year	US	Europe	EU-15	EU-25
Share of patents (by inventor nationality)					
Pharmaceutical	1974-2003	57.32		26.80	
Biotechnology	1974-2003	60.1		24.26	
Medical Devices	1974-2003	73.5		13.37	13.5
Pharmaceutical	1994-2003	59.62		25.64	
Biotechnology	1994-2003	63.15		22.35	
Medical Devices	1994-2003	74.3		13.35	13.44
Share of patents (by assignee nationality)					
Pharmaceutical	1974-2003	57.32		n.a.	n.a.
Biotechnology	1974-2003	60.1		n.a.	n.a.
Medical Devices	1974-2003	74.6		12.37	12.51
Pharmaceutical	1994-2003	59.62		n.a.	n.a.
Biotechnology	1994-2003	63.15		n.a.	n.a.
Medical Devices	1994-2003	75.54		11.76	11.85
Share of citations (by assignee nationality)					
Pharmaceutical	1974-2003	71.4		5.52	
Biotechnology	1974-2003	77.4		12.35	
Medical Devices	1974-2003	81.43		9.04	9.13
Pharmaceutical	1994-2003	74.3		16.02	
Biotechnology	1994-2003	89.0		4.79	
Medical Devices	1994-2003	84.7		7.54	7.58
R&D licensing agreements					
Pharmaceuticals (% as licensor)	1991-2003	69.15	21.19	19.57	19.65
Pharmaceuticals (% as licensee)	1991-2003	60.87	26.79	22.25	22.34
Medical Devices (% as licensor)	1991-2003	73.76	17.16	15.33	15.37
Medical Devices (% as licensee)	1991-2003	71.5	19.94	15.63	15.72
Publications					
Pharmaceutical Preparations	1984-2003	44,193		43,514	45,948
Ratio over US publications		*1.00*		*0.98*	*1.04*
Equipment and Supplies	1984-2003	99,693		94,095	96,403
Ratio over US publications		*1.00*		*0.94*	*0.97*

1. INTRODUCTION AND STRUCTURE OF THE STUDY

This Study on "medical devices: competitiveness and impact on public health expenditure" contributes to the implementation of Article 157 of the treaty establishing the European Community. Title XVI ("Industry") of the article states that: "*The Community and Member States shall ensure that the conditions necessary for the competitiveness of the Community's industry exist*" and that "*For that purpose, in accordance with a system of open and competitive markets, their action shall be aimed at fostering better exploitation of the industrial potential of policies of innovation, research and technological development*".

Besides being a vital and innovative industry, medical devices are a key component of healthcare systems and represent, together with pharmaceuticals, the bulk of "medical technology". Technological progress in medical care has been the main driver of improvements in healthcare systems in order to prevent, diagnose and treat diseases, as well as enhancing health status and quality of life. Yet at the same time, medical technology is often quoted as one of the main reasons behind increasing healthcare costs and expenditure.

The analysis of the sector must therefore investigate medical devices as an industry – an innovative contributor to the economy – as well as offering a key input to healthcare systems. The links between these two aspects which involve health institutions, policies and regulations, also need to be assessed.

This Study aims to provide a coherent analytical overview of the state of the EU medical device industry covering the following issues:

I. The impact of innovation in medical devices on health costs and expenditure;

II. The innovativeness of the European medical device industry;

III. The competitiveness of the European medical device industry as compared to the United States and Japan.

Furthermore, the Study provides suggestions on how to overcome the current statistical shortcomings that represent a severe limitation to the possibility of implementing a coherent and unified framework for policy awareness and intervention at an EU level.

In so doing, the Study clearly distinguishes between "medical devices" and "medical technologies". Medical technologies include medical devices as one of its constituents, and can be defined as "*the drugs, devices and medical and surgical procedures used in medical care, and the organisational and supportive systems within which such care is provided*" (OTA, 1984).

The reference concept and definition for medical devices in the Study is the one adopted in the European Union Medical Devices Directive (93/42/ECC), article 1, which covers "*any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:*

- *diagnosis, prevention, monitoring, treatment or alleviation of disease;*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;*
- *investigation, replacement or modification of the anatomy or of a physiological process;*
- *control of conception;*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by

such means."[1] In vitro diagnostics (IVD) are covered by the Study in the definition and concept adopted in the In Vitro Diagnostic Medical Devices Directive (98/79/EC), where IVD are defined as "*any medical device which is a reagent, reagent product, calibrator, control material, kit instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information: concerning a physiological or pathological state; or concerning a congenital abnormality; or to determine the safety and compatibility with potential recipiens; or to monitor therapeutic measures".*

BOX 1: Examples of medical devices

- Anaesthetic machines and monitors
- Apnoea monitors
- Artificial eyes
- Artificial limbs
- Blood transfusion and filtration devices
- Breast implants
- Cardiac monitors
- Cardiopulmonary bypass devices
- Clinical thermometers
- Condoms
- Contact lenses and prescribable spectacles
- CT scanners
- Defibrillators
- Dental equipment and dentures
- Dental material and restoratives
- Diagnostic imaging equipment
- Diagnostic kits and tests
- Dialysers
- Electrosurgery devices
- Endoscopes
- Enteral and parenteral feeding systems
- Equipment for disabled people
- Examination gloves
- Foetal monitors
- Hearing aids and inserts
- Heart valves
- Hospital beds
- Hydrocephalus shunt
- Incontinence pads
- Infusion pumps and controllers
- Intra-uterine devices
- Intravascular catheters and cannulae
- Laboratory equipment
- Lithotripters
- Medical lasers
- Medical textiles, dressings, hosiery and surgical supports
- Orthopaedic implants
- Operating tables
- Ostomy and incontinence applicances
- Pacemakers
- Physiotherapy equipment
- Prescribable footwear
- Pressure sore relief devices
- Radiotherapy machines
- Resuscitators
- Scalpels
- Special support seating
- Sphygmomanometers
- Stents
- Suction devices
- Surgical instruments and gloves
- Sutures, clips and staples
- Syringes and needles
- Ultrasound imagers
- Urinary catheters, vaginal speculae and drainage bags
- Ventilators
- Walking aids
- Wheelchairs

Source: Healthcare Industry Task Force (2004).
Note: the list is not exhaustive and is intended to illustrate the range of of products manufactured by the industry.

Nevertheless, in some sections of the Study it has been necessary to adopt broader or narrower definitions of medical devices, in order to address specific issues or, for the empirical analysis, to account for data availability. Departures from the EU Directive definition of medical devices are always highlighted and circumstantiated.

The framework and objectives outlined above are developed along nine chapters:

- **Chapter 1: Introduction and structure of the Study**.
- **Chapter 2: The medical technology marketplace at the macro level**. This chapter defines the broad picture and provides an overview of the world and European medical device markets. Throughout this chapter, the medical device industry is put in perspective by

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highlighting its role as a component of national healthcare systems on the one side, and of industrial systems on the other.

- **Chapter 3: Long term trends of health expenditure and the impact of new technologies**. This chapter illustrates the relationship between technological change in medicine and health expenditure, first from a theoretical point of view, and then through the review of a large number of empirical studies on the subject. It finally frames the issue of the sustainability of medical device innovations into the debate on social expenditure composition and overall reform.
- **Chapter 4: Economic evaluation of medical devices: some case studies**. The objective of this chapter is to present some examples of the impact of medical device innovations on the whole health system. In most of the cases, Chapter 3 reveals at the aggregate level evidence of a significant effect of innovation in medical technology on health costs and expenditure. However, at the micro level, single innovations have proven to save healthcare resources, mainly through the reduction of hospitalisation, early detection and diagnosis of diseases and syndromes, reduction of invasiveness of medical intervention, and improvement of citizens' quality of life. Costs/expenditures constitute only one of the economic dimensions on which innovation produces its impact. Medical innovations need to be evaluated with respect to either the *effectiveness* of the innovation (as measured by clinical indicators) or its *benefits* (in terms of utility, specified in various ways).

  In this chapter, some case studies of major technological innovations in medicine are set out. The aim of this exercise is to expand the reference scenario in order to illustrate the net effect of innovation in medical devices when the effectiveness factor and the societal perspective (that includes quality of life aspects) are taken into account.

  Four case studies are investigated:

  a) Interventional cardiology market: drug eluting stents;

  b) Diabetes treatment and blood glucose control;

  c) Osteoarthritis and total hip replacement;

  d) Imaging devices for mammography.

  The analysis of specific examples of major innovation in the medical device industry helps us in identifying key aspects that are functional to the following sections of the Study, such as the extent and heterogeneity of the knowledge base on which the innovation processes draws upon, the post-launch market dynamics of innovative products, and the properties and structure of the reference markets.
- **Chapter 5: Productivity, competitiveness and industry structure**. In Chapters 5 and 6, the focus shifts to medical devices as an industry, in order to identify its structural characteristics and international competition dynamics.

  The industry structure is analysed in terms of size distribution and diversification within and between medical device sub-markets. In addition, the main competitiveness indicators – production, productivity, value added, and trade indicators – are presented for the relevant aggregates (EU, US and Japan), and the relative competitiveness of the different industries are assessed.

  This chapter shows that the European medical device industry is lagging behind the US, both in terms of production capabilities and international competitiveness.

  Even though the analysis of product flows between countries shows the leading role of the US on the international scene, European firms hold a competitive position in most of the diagnostic equipment segment of the industry. However, as European firms are smaller and

less diversified than US counterparts, they are likely to experience more constraints in accessing resources and financing for innovation and internationalisation.

- **Chapter 6: R&D and innovation**. This chapter analyses different aspects of the European innovation system in the medical device industry from R&D to the uptake and diffusion of medical innovations. This analysis is performed in order to assess the level of innovativeness of the European medical device industry as compared to the US and Japan. Patent analysis highlights the key role played by small firms and individuals in the medical device innovation process and the high level of heterogeneiety of the relevant knowledge bases. European firms lag behind their US counterparts in terms of R&D intensity. However, it is worthwhile noticing that R&D intensity varies considerably among Member States and sectors of the medical device industry with some countries (Germany and France) and sectors (in-vitro diagnostics on above all) that show a high level of R&D intensity. The analysis of the market for medical technologies confirms the pivotal role of the US system even if Europeans still hold a comparative advantage in technologies related to implantable devices, and therapeutic equipments and supplies.

  All in all, Chapters 5 and 6 show that the European medical device industry is less innovative and competitive than the US one.

- **Chapter 7: Statistical shortcomings for the sector: analysis and proposals**. The lack of a systematic effort at the international level to collect, integrate, update and diffuse primary data and information on the state and the evolution of the medical device industry represents a severe limitation to this Study as well as to previous analytical efforts. Data limitations also dramatically reduce the efficacy of public policies to enhance the competitiveness and productivity of the EU medical device industry, and the development of a European system of innovation. After describing the main characteristics and shortcomings of the available data sources at the international level, Chapter 7 proposes a statistics framework for the implementation of a data collection strategy for the European medical device industry.

  First of all, single national offices of statistics, regulatory bodies and international institutions urge the identification of a common definition for the sector and an industry classification of medical device sub-sectors based on both market and technological factors.

  Secondly, national offices of statistics of Member States and Eurostat should adopt the same classification and provide disaggregated figures for relevant segments of the medical device industry.

  Finally, regulatory bodies and public institutions in general should provide private incentives to collect micro-level data on the industry and market structure and strengthen their efforts to harmonise data and information at the EU level.

- **Chapter 8: Policy recommendations**. This chapter proposes strategic recommendations to the European Commission and Member States on policy options for the sector, identified on the basis of the analysis of the previous chapters. The starting point for this activity has been the recognition of the inherent complexities of the sector, as highlighted in this Study, whereby a heterogeneous and vital innovative industry is also a component of healthcare systems. This means that no easy-menu exists for policies aimed at controlling costs while enhancing the quality of health services, innovation and competitiveness. The endorsement of these distinct objectives involves trade-offs and difficult resource allocation decisions. Indeed, the clear recognition and political statement of these distinct objectives and the trade-offs can be considered as a policy recommendation *per se*.

  The main policy issues, options and recommendations to Member States and the European Commission are identified and presented with regard to: a) reconciling the objective of expenditure control with the improvement of healthcare performance through new

technologies; b) preserving and enhancing the innovativeness of the European medical device industry and, more generally, c) its competitiveness in the world market.

2. THE MEDICAL DEVICE MARKETPLACE AT MACRO LEVEL

Summary of the chapter

This chapter provides an overview of the worldwide and European medical device sector, and puts it in perspective by highlighting its role as a component of national healthcare systems, on the one side, and of the industrial systems on the other.

The worldwide medical device market in 2003 is valued at over €184 billion - US$220 billion, with an estimated nominal increase of about 16 percent from the previous year. The US constitutes the largest world market for medical devices, representing a world share of 38-43 percent. The European market, at 30-34 percent of the world share, is the second largest market, followed by Japan. The rest of the world market represents 14-16 percent of the global market. Within Europe, Germany is the leading market, followed by France, Italy and the UK. The two largest markets, Germany and France, account for half of the European market, and the four largest accounts for over 70 percent of it.

Medical devices are a key component and input to health systems. In Europe, 6.2 percent of total health expenditure goes on medical devices (with health expenditures accounting on average for 7.8 percent of the GDP). Both the US and Japan spend some 5.1 percent of total health expenditure on medical devices (with health expenditures accounting for respectively 13.9 and 7.6 percent of GDP). The data on per capita expenditure on medical devices (calculated using the purchasing power parity correction) show the US with the highest per capita expenditure, at €278 in 2002; the figures for the EU-15 and Japan are less than half the figure for the US, at respectively €124 and €136. The data available for the EU new Member States reveal significantly lower per capita expenditure than that for the EU-15.

Medical devices are also an important part of the EU manufacturing sector. Data available for a subset of the total aggregate show that the they constitute at least 0.8 percent of total production of the EU-25 manufacturing sector and 1.2 percent of total EU-25 manufacturing employment.

Despite growing pressures from national cost-containment policies that have curbed the positive trend of growth of the sector, the industry is extremely vital, driven by growing income, aging populations and in general societies' commitment to improving the quality of life. In the EU-25, medical device production has recorded top growth rates in recent years (12.5 percent in 2001 and 7.8 percent in 2002), well above the average of the manufacturing sector (1.8 percent and 0.3 percent). The good outlook for the sector is confirmed by its positive performance in the stock markets, where medical devices have systematically outperformed the average market trend.

2.1 Medical device markets

The medical device aggregate is composed of a wide range of different products, and is therefore difficult to quantify. As a consequence the figures presented in this chapter come from a multitude of heterogeneous sources – national and official statistics, companies, industry associations, market intelligence firms – and have not been fully validated and should be interpreted as illustrative only. The lack of a harmonised cross-country data collection standard, on a global and EU level, severely restricts the possibility of mapping the industry at the international level and of making

comparisons[2]. All these circumstances should prompt the reader to be careful when making comparisons across countries, markets and over time.

Global markets

The worldwide medical device market in 2003 is valued at over €184 billion - US$220 billion (Eucomed 2004; Standard & Poor's, 2004a), a nominal increase of about 16 percent from the previous year (Standard & Poor's, 2004a).

Table 1. Medical device world market

Standard & Poor's	Eucomed
2003: $220 bill	2003: > €184 bill
2002: $190 bill	2002: > €184 bill

Source: Eucomed (2003; 2004), Standard & Poor's (2004a).
Note: definition of medical devices for each source in footnote[3].

Medical device products can be grouped into medical high-tech products and more conventional products. The segment of high tech products is composed of sophisticated devices designed for specific therapeutic and diagnostic uses. These are associated with costly and risky R&D activities, clinical trials, administrative and regulatory procedures for marketing clearance. Products from this segment have strong growth potential and are at significant risk of becoming obsolete. For companies specialising in the high-tech sector, new products (those introduced within the preceding two years) typically account for more than 30 percent of sales (Standard & Poor's, 2004a). However, it must be noted that for some companies new products introduced within the preceding 12 months account for more than 60 percent of sales. The market of more conventional devices consists of items such as syringes, gauze, and intravenous products as well as a wide range of other conventional diagnostic and therapeutic products. This segment is associated with low margins and high volumes.

The US market constitutes the largest world market, representing a share estimated at 38-43 percent. The European market, at 30-34 percent of the world share, is the second largest market, followed by Japan. The rest of the world market represents 14-16 percent of the global market (see Table 2).

[2] "… *As there is little reliable data on the* (medical devices) *industry, the figures used in this study came from a number of different sources. As a result, there are inconsistencies which cannot be easily reconciled…*" (UK Healthcare Industries Task Force, 2004, page 15).

[3] Definitions of the medical devices aggregate:

- Eucomed: the reference definition corresponds to that of the EU Medical Devices Directive (93/42/ECC); the figures are from Eucomed's calculations and estimations based on their data sources, reported in Eucomed (2003, see the Appendix; or at http://www.eucomed.be/docs/Overview%20sources.pdf).
- Standard & Poor's: "*..include commodity-type items such as kits, trays, gloves, gowns, syringes, and other disposable medical supplies, as well as higher technology products, among which are infusion and related intravenous supplies and equipment, diagnostic and laboratory products, wound-management supplies, orthopaedic reconstructive implants, spinal devices, surgical devices, cardiac products, and diagnostic equipment*."

Table 2. Shares of medical device world market, 2002

	Eucomed		Datamonitor	
	Expenditure (€bill)	Share	Expenditure ($ bill)	Share
Europe	55	30	63	34
US	79	43	71	38
Japan	20	11	25	13
Rest of the world	30	16	26	14
World	184	100	186	100

Source: Datamonitor (2003a), Eucomed (2003).
Note: Datamonitor definition of medical devices in footnote[4]

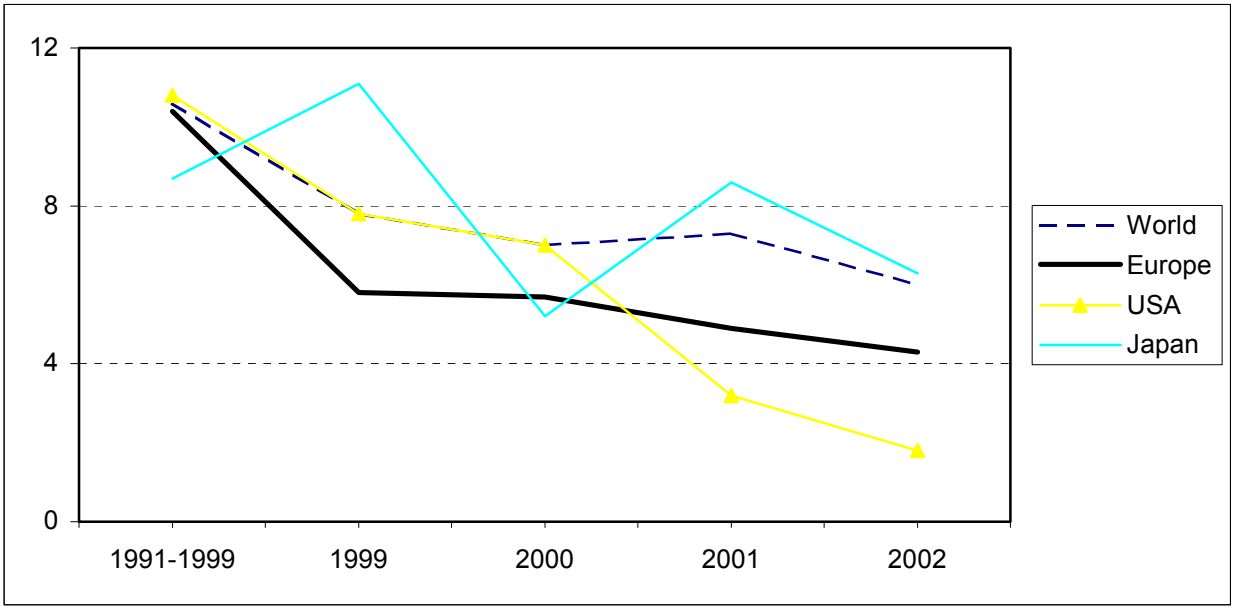
As will be seen in the next chapter, demographics (aging population), income growth (that can sustain increasing demand for high-tech health services) and increasingly extensive health insurance systems, are regarded as long-term drivers of the medical device market. These factors have sustained strong market growth for medical devices in the past years and decades. In recent years, cost-containment policies adopted by increasingly cost-conscious healthcare systems and providers affected by growing budget deficits have put medical device markets under pressure in most countries.

In Europe, large budget deficits have pressured Governments to lower healthcare spending and, together with it, spending on medical devices and associated medical procedures. In the US, markets have registered the restrictive impact of the expansion of managed care in the healthcare marketplace, that at present account for about 70 percent of all medical device purchases in the US. Managed care providers use their purchasing power to obtain discounts on bulk purchases of medical products, and employ various typologies of gatekeepers to direct access to diagnosis or therapeutic procedures based on medical devices. Government efforts to control healthcare spending are heavily affecting the medical device market also in Japan. In the 2000 biennial price revision of the reimbursement prices for medical devices, an average price reduction of 4.5 percent was implemented for three major categories (arterial catheters, pacemakers and orthopaedic implants), and in 2002 a new pricing policy on implants was instituted, which includes reimbursement cuts based on foreign reference pricing.

Market dynamics for the major market reflect the evolving interaction of these driving factors: Figure 1 shows the long-term growth of the industry, and its contraction in recent years, explained by most analysts as the result of the intensification of national cost-containment policies.

[4] Health care equipment and supplies "*include active implants, aids for the disabled, anaesthetic & respiratory devices, dental devices, drug delivery systems, emergency medical equipment, electro-medical devices, hospital equipment, imaging & radiotherapy devices, ophthalmic & optical devices, passive implants, single use disposables, and surgical instruments*". Market value is calculated at manufacturers selling price.

Figure 1. Growth of medical device major markets (%)



Source: AdvaMed (2004)[5]; Datamonitor (2003a).

European market

The European medical device market for 2002 is estimated at €55 billion-$63 billion. Within Europe, Germany is the leading market, followed by France, Italy and the UK. The two largest markets, Germany and France, account for half of the European market, and the four largest account for over 70 percent of it.

Table 3. European medical device markets ranked by size, 2002

	Expenditure (€mil)	Share
Germany	19,000	34.4
France	9,000	16.3
Italy	6,160	11.2
United Kingdom	5,800	10.5
Spain	3,000	5.4
Netherlands	2,500	4.5
New EU Member States	1,950	3.5
Switzerland	1,360	2.5
Sweden	1,080	2.0
Norway	930	1.7
Denmark	870	1.6

[5] Data for the US do not account for outsourcing/off shoring where a manufacturer is manufacturing finished products in another country.

	Expenditure (€mil)	Share
Belgium	820	1.5
Austria	730	1.3
Portugal	600	1.1
Greece	540	1.0
Finland	450	0.8
Ireland	360	0.7
Luxembourg	50	0.1

Source: Eucomed (2004); most but not all figures refer to year 2002.

The ten new Member States account as a whole for 3.5 percent of the European market, of which 77 percent is represented by Poland, Czech Republic and Hungary.

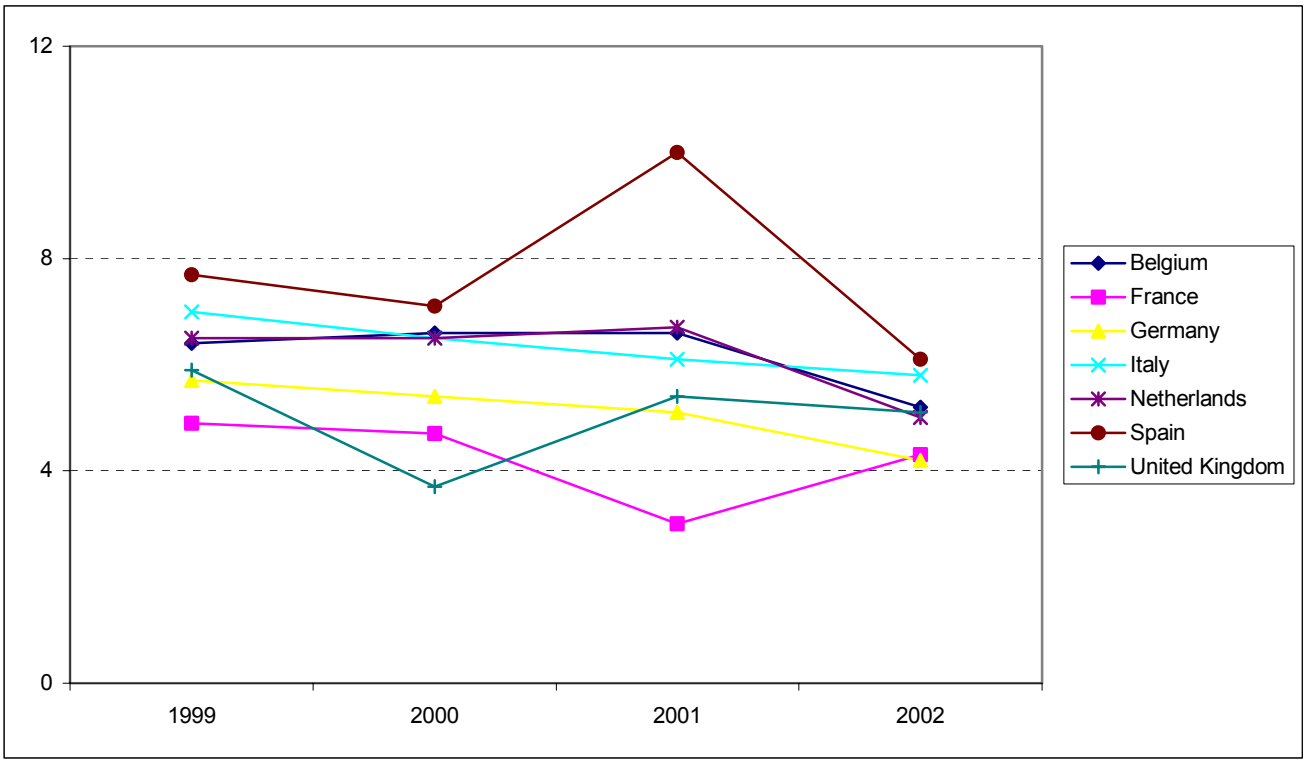
Table 4. EU new Member States' markets for medical devices ranked by size, 2002

	Expenditure (mil €)	Share
Poland	770	39.5
Czech Republic	370	19.0
Hungary	360	18.5
Slovenia	130	6.7
Slovak Republic	110	5.6
Latvia	60	3.1
Lithuania	60	3.1
Estonia	40	2.1
Cyprus	30	1.5
Malta	20	1.0

Source: Eucomed (2004); most but not all figures refer to year 2002.

The recent market contraction seen in Figure 1 is shared by most European countries, as can be seen from Figure 2 for a selection of countries (for which data is available).

Figure 2. Growth (%) of selected European markets of medical devices



Source: Datamonitor (2003a).

The decline in the growth rate is noticeable for most sub-markets for which data is available, but has affected the different segments with heterogeneous intensity, as can bee seen from Table 5.

Table 5. Growth (%) of selected sub-markets in Europe

	1999	2000	2001	2002	2003
Computed tomography	n.a.	18	41	18	3
Magnetic resonance	n.a.	4	36	15	-4
Ultrasound	n.a.	15	19	13	12
X-ray	n.a.	21	-9	9	-13
Radiology information systems (RIS) and picture archiving and communications systems (PACS)	n.a.	n.a.	n.a.	25	15
In vitro diagnostics	3.8	4.6	7.3	6	5.6
Orthopaedics	7	9	12	16	n.a.
Dental	n.a.	17	-6	12	-10

Sources: COCIR (for computer tomography, magnetic resonance, ultrasound, X-ray, RIS and PACS); EDMA (2004; for in vitro diagnostics); ADDE & FIDE (2004; for dental); our estimates based on Datamonitor (2003b) and discussions with the industry (for orthopaedics) [6].

[6] Computed tomography, magnetic resonance, ultrasound, X-ray: data only for France, Germany, Italy, UK (including Ireland from 2003); surveyed sample growing over time.
- RIS and PACS: Europe is EU-15 plus the following: Switzerland, Norway, Turkey, Czech Republic, Hungary, Poland, Russia.
- In vitro diagnostics: data for 14 European Countries, including Romania and Poland.
- Dental: surveyed countries exclude all new Member States but Czech Republic.
- Self-monitoring of blood glucose: data on volumes.

Durable large-scale equipment in particular appears to have suffered from intensified pressures to hold down costs. For instance, despite technological development resulting in diagnostic superiority compared to previous imaging techniques for magnetic resonance imaging, purchasers are hesitating to invest because of the difficulty to get a reimbursement for the funding for capital investment.

Orthopaedic devices hold the trend firmly. These devices are used for the repair and replacement of skeletal problems and include products such as artificial body parts, joint replacement, products used for repairing broken bones, devices for spinal column repair and arthroscopic equipment for vision during procedures. The growth of the segment is believed to be strongly sustained by the phenomenon of an aging population and by the increasing demand for a better quality of life that involves implantable products for reconstruction in the hip, knee and spine (Standard and Poor's, 2004a).

The in vitro diagnostic segment (IVD) produces the analytical instruments and the reagents that are used to perform various tests for diagnosis as well as for the monitoring and management of diseases. Behind the aggregated figure in Table 5, are different sub-sector trends: cardiac markers, glucose testing, nucleic acid-based reagents have experienced in recent years two-digit rates of growth; conversely, other sub-sectors, such as microbiology are suffering. Some analysts suggest that the growth in the market segment of diabetes testing and cardiac markers is related to the increasing awareness of the economic and clinical benefits of IVD testing in these areas.

The sub-market of radiology information systems (RIS) and picture archiving and communication systems (PACS) shows two-digit growth rates, and is predicted to maintain a solid growth in the near future (TekPlus, 2002). The development of RIS and PACS has been the result of the need to store and manage the usage of the increasing number of images produced by different diagnostic scanners (computed tomography, magnetic resonance and nuclear imaging and others). The expansion of the sector, already well established in the US, is predicted to involve Europe in the next few years. Here, providers are now moving to a film-less environment, and governments have announced massive investments to enhance the efficiency of health systems through the injection of the processes of information technology tools (The Economist, 2005).

2.2 Medical device expenditure as a component of European Union health systems

European Countries spend on average 7.8 percent of GDP on health. This figure is on average higher for the EU-15 aggregate (8.3 percent) than for the new Member States (6.6 percent), and compares with a 13.9 percent for the US and a 7.6 percent for Japan.

In Europe, 6.2 percent of total health expenditure goes to medical devices. This percentage is higher for new Member States (7.6) than for the EU-15 aggregate (5.4 percent). Both the US and Japan spend some 5.1 percent of total health expenditure on medical devices.

The data on per capita expenditure on medical devices calculated with the purchasing power parity correction (PPP; here with respect to the US dollar), a procedure that takes into account the cost of living differentials across different countries, show a high degree of heterogeneity between and within areas. The US reports the highest per capita expenditure, at €278; the figures for the EU-15 and Japan are less than half of that, at respectively €124 and €136. The data for the EU new Member States reveal significantly lower per capita expenditure than for the EU-15.

Table 6. Indicators of expenditure in medical devices, 2002

	MD expenditure as a % of total health expenditure	Total health expenditure as a % of GDP	MD expenditure per capita (€)	MD expenditure per capita (€) at US$ PPP
Austria	4.3	7.9	90	101
Belgium	3.6	9.0	79	92
Denmark	5.7	8.6	161	147
Finland	4.8	7.0	86	90
France	6.5	9.5	150	175
Germany	8.6	10.7	230	246
Greece	4.4	9.4	49	74
Ireland	4.9	6.5	89	93
Italy	5.8	8.6	107	133
Luxembourg	4.1	5.6	111	115
Netherlands	6.5	8.9	154	172
Portugal	5.3	9.2	57	89
Spain	6.1	7.5	73	100
Sweden	5.1	8.7	120	121
United Kingdom	4.8	7.6	97	103
Cyprus	4.5	6.1	41	n.a.
Czech Republic	7.9	7.3	36	80
Estonia	10.8	5.8	30	n.a.
Hungary	9.2	6.8	36	78
Latria	11.5	5.8	26	n.a.
Lithuania	8.3	5.7	17	n.a.
Malta	1.7	8.8	50	n.a.
Poland	6.1	6.3	20	43
Slovak Republic	8.6	5.7	20	55
Slovenia	7.1	8.0	65	n.a.
Norway	6.2	8.0	206	174
Switzerland	4.5	11.1	188	154
EU-15 average	5.4	8.3	134	124
New Member States average	7.6	6.6	26	n.a.
EU-25 average	6.2	7.6	116	n.a.
Europe average	6.2	7.8	118	n.a.
US	5.1	13.9	278	278
Japan	5.1	7.6	158	136

Source: Our calculation based on Eucomed (2003; 2004); most but not all figures refer to year 2002.

Notes: PPP values calculated through the 2002 GDP PPP exchange rate with the US$ (OECD Health Data, 2004).

As Table 6 shows, the picture within the EU is quite heterogeneous, reflecting among other things different national choices towards the organisation and size of the health sector. Member States have full responsibility for this area, and "*...European Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care. The responsibilities of the Member States shall include the management of health services and medical care and the allocation of the resources assigned to them*. …" (EU Constitution, Chapter V, Section I "Public Health").

The heterogeneity in national choices on health system and organisation reflected in Table 6, is mirrored in Table 7, which shows cross-country penetration of a number of medical devices and use of high-technology medical procedures. No "technology-champions" can be identified among Member States when looking at the number of high-tech medical devices and procedures. Systems use different mixes of diagnostic and curative practices according to national protocols and medical standards. The ways in which various health systems in European countries organise and finance their medical technologies are influenced by a combination of factors that include the nation's historical precedents, consumer pressures, country income, health infrastructures, market structure and the level of competition among providers (and factors affecting it).

On an international level, the high endowment of Japan with imaging devices – MRI and especially CT - is remarkable, especially when considering that the country devotes a lower amount of resources (in GDP) that the EU (15) and the US to the health sector. The use rate of dialysis in Japan is also by far the largest of the countries listed in the table. On the other side, the US high propensity to perform high-tech medical procedures exceeds that of most other countries.

Table 7. Medical devices and medical technology penetration

	Magnetic resonance imaging units (MRI)/ mill. pop.	Computed tomography (CT)/ mill. pop.	Radiation therapy equipment/ mill. pop.	Mammographs/ mill. pop.	Patients with dialysis/ 100 000 pop.	Cardiac catheterisation procedures/ 100 000 pop.	Coronary stenting procedures/ 100 000 pop.	Heart transplant procedures/ 100 000 pop.	Kidney transplant procedures/ 100 000 po.
year	**2002**	**2002**	**2002**	**2002**	**2002**	**2001**	**2001**	**2001**	**2001**
Austria	13.4	27.3	4.5	n.a.	39.2	482.1	n.a.	0.8	5.2
Belgium	n.a.	n.a.	n.a.	n.a.	n.a.	464.7	118.2	1.1	3.5
Czech Republic	2.2	12.1	9.2	13.2	n.a.	n.a.	n.a.	0.5	3.2
Denmark	8.6	13.8	6	n.a.	43.9	328.9	56.7	0.6	3.0
Finland	12.5	13.3	8.8	39.6	25.7	n.a.	n.a.	0.3	3.3
France	2.7	9.7	6	42.4	58	387.7	124.7	0.5	3.4
Germany	n.a.	13.3	10.6	n.a.	67.7	n.a.	n.a.	0.5	2.9
Greece	2.4	17.7	n.a.	29	71.9	207.2	50.8	0.0	1.5
Hungary	2.5	6.8	n.a.	n.a.	n.a.	559.3	n.a.	0.1	2.6
Ireland	n.a.	n.a.	n.a.	n.a.	n.a.	134	52.1	0.3	3.1
Italy	10.4	23	3.8	n.a.	n.a.	35.9	10.4	0.5	2.7
Luxembourg	4.5	24.7	4.5	22.4	81.4	353.1	n.a.	n.a.	n.a.
Netherlands	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.2	3.3
Portugal	n.a.	n.a.	n.a.	n.a.	74.7	108.5	28.9	0.2	3.5
Slovak Republic	2	10.6	13.2	12.1	43.1	n.a.	n.a.	0.1	1.9
Spain	6.2	12.8	3.6	n.a.	n.a.	n.a.	n.a.	0.8	4.7
Sweden	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.3	3.5
United Kingdom	4	5.8	3.3	n.a.	33.4	6.5	n.a.	0.3	2.9
United States	8.2	12.8	4	11.9	n.a.	414.7	165.4	0.8	5.0
Japan	35.3	92.6	6.6	n.a.	180.2	n.a.	n.a.	n.a.	0.6

Source: OECD Health Data (2004).

2.3 Medical devices as a component of the European Union industrial system

The medical device industry is an important contributor to the European Union manufacturing sector. Reliable data for assessing the position of the industry exist only for a subset of the medical device aggregate as defined by Directive 93/42. Eurostat provides figures on "Medical and surgical equipment and orthopaedic appliances" (NACE DL 33.1). This aggregate does not include, among others, high-tech chemical and biochemical-based devices such as in vitro diagnostics (that are grouped instead under "chemicals") and medical-impregnated products such as gauzes and bandages (that are under "pharmaceutical preparations"). The inadequacy of the NACE classification in representing the whole medical device sector will be considered in Chapter 7. Here it is important to point out that the following data under-represent the sector, in magnitude and high-tech intensity.

The manufacture of medical devices (medical and surgical equipment and orthopaedic appliances) generated in 2001 value added for €17.2 billion in the EU-25, from a turnover of €41.3 billion. The workforce in this sector was of about 350,000 workers. As such, the contribution of the sector was 1.1 percent of total EU-25 manufacturing value added and 1.3 percent of total EU manufacturing employment.

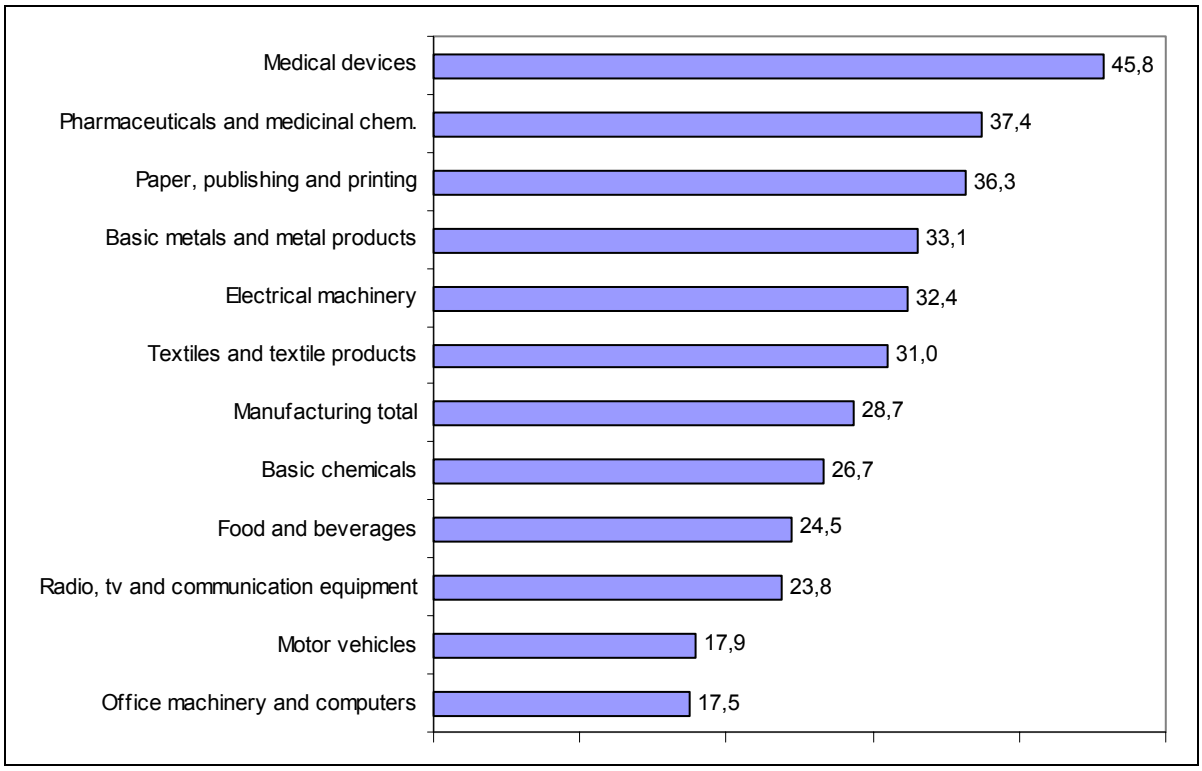
Table 8. Medical devices (NACE DL 33.1) in the EU-25 manufacturing sector, 2001

		as a % of total EU-25 manufacturing
Value added	€17.2 billion	1.1
Employment (units)	352,000	1.2

Source: Eurostat (2004a).

At the industry level, value added is the value of industry firms' output minus the value of all the inputs purchased from firms of other sectors. Therefore, it represents a measure of the profit earned by a particular firm plus the wages it has paid i.e. the value of the labour and capital the industry uses. In the EU, medical devices are a top generator of value added compared to other manufacturing sectors: Figure 3 shows that almost 46 percent of the value of production is generated within the industry through the manufacturing process. This reflects the high value of the labour and capital the industry uses.

Figure 3. Value added created as a percentage of production value

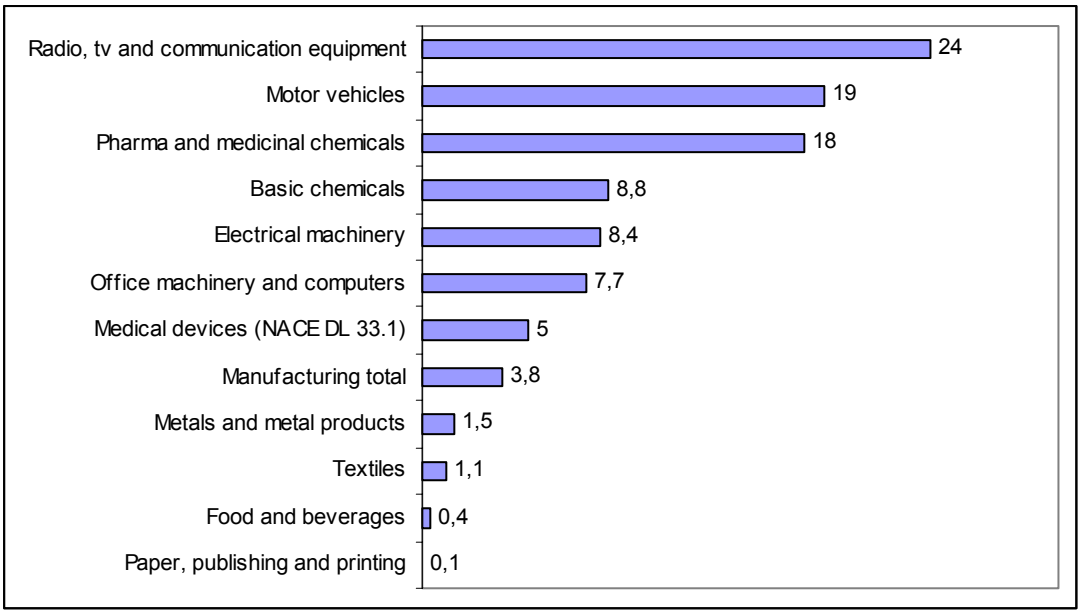


Source: Eurostat (2004a).

The medical technology industry is R&D intensive. As it will be seen in Chapter 6, in the innovation process for medical devices, more than for most other industries, many fields of science converge. In addition, innovation for the sector is incremental, and is conducted both in-house to the manufacturer and at the clinical level, whereby physicians refine technologies through iterative experience. While being applicable to many healthcare technologies, the standard model of "linear and unidirectional innovation" (Gelijins and Rosenberg, 1994) – where basic research is input to applied research, which leads to development, manufacturing, marketing and finally adoption of a finished product – does not apply to medical device innovation. As a consequence, innovation processes and efforts for the industry are difficult to track and quantify, and standard measures, such as intramural R&D activities, can reflect only to a limited extent the innovative intensity and efforts for the industry (Gelijins and Rosenberg, 1994).

Figure 4 depicts the R&D intensity of the medical device sector, and its relative position compared to other manufacturing sectors. Medical devices show a higher R&D intensity (5 percent of value added) than total manufacturing sector (3,8 percent of value added), but significantly lower than several other manufacturing sectors. The considerations above, and the absence within the NACE DL 33.1 aggregate of high-tech innovative products, determine an under-representation in these data of the R&D efforts of the sector.

Figure 4. Share of R&D in value added (%)



Source: Eurostat (2004a).

Even during the recent years of economic slowdown the industry has kept its pace. In the EU-25 medical devices, together with pharmaceuticals, have recorded in 2001 and 2002 the highest production growth rates, while several sectors were showing negative figures (Table 9).

Table 9. EU-25 growth rates for selected industries, %

	2000	2001	2002
Pharma and medicinal chemical	n.a.	7.9	11.6
Medical devices (NACE DL 33.1)	n.a.	12.5	7.8
Food and beverages	1.7	6.7	0.7
Maufacturing total	9.5	1.8	0.3
Paper. publishing and printing	10.3	-1.1	-0.3
Basic chemical	n.a.	-1.9	-0.3
Metals and metal products	9.9	0.3	-1.0
Textiles	3.3	0.5	-3.0
Electrical machinery	11.0	3.2	-4.5
Radio, tv and communication equipment	32.6	-13.7	-12.3
Office machinery and computers	13.5	-4.0	-18.1

Source: Eurostat (2004a).

The positive outlook for the sector is reflected in its performance on the stock market, where it has systematically outperformed the market average trend. Despite growing pressures from public budget problems, the fundamentals of the industry remain strong, driven in the major markets by the aging population that increasingly requires and demands medical procedures. The Morgan Stanley Healthcare Equipment and Supplies World Index gained 24 percent between September 2003 and September 2004[7], outperforming the Morgan Stanley World Index (that reflects the world stock market performance) that was up 12.3 percent in the same period. The Healthcare Equipment

[7] Precisely from 30 Sept. 2003 to 30 Sept. 2004.

and Supplies sector outperformed the market in all geographic areas. In recent years, the companies traded on the European stock markets performed better than their counterparts traded in the US and Japan, as shown at the bottom of the diagram.

Most financial analysts agree on the view of a persisting positive fundamental outlook and continuing growth for the sector, driven by favourable demographics and under-penetration of key procedures. Nevertheless, future growth is predicted at a slower rate than in the past years (Morgan Stanley, 2004; Standard and Poor's 2004a; Credit Suisse First Boston, 2004).

3. THE MEDICAL TECHNOLOGY - HEALTH EXPENDITURE LINK: THEORY AND EMPIRICAL EVIDENCE

Summary of the chapter

This chapter illustrates the relationship between technological change in medicine and health expenditure, first from a theoretical point of view, and then through the review of a large number of empirical studies on the subject. It finally frames the issue of the sustainability of medical device innovations into the debate on social expenditure composition and overall reform.

Simple models that show the static impact of innovations on the demand and supply of medical care, do not determine *a priori* the overall net impact of technological progress on health expenditure, i.e. the result of the interplay of factors that may point to opposite directions. More complex frameworks of analysis have included institutional arrangements such as the provision of institutional health insurance in a dynamic context. These show that the long-run growth of healthcare expenditure is a by-product of the self-fulfilling interaction between expanding insurance and the development of new technologies.

In general, both static and dynamic frameworks of theoretical analysis provide mixed indications on the medical technology–health expenditure link: the effect of cost-reducing technologies, increasingly incentivised by constrained health insurers, could in principle offset the demand-side effect and the self-fulfilling interaction. It is then necessary to switch to empirical analysis in order to collect evidence on the dynamics highlighted above, and on the sign of the link.

To this end, economic and medical literature has been extensively researched and reviewed. This assessment shows that although single new technologies may exert both upward and downward pressures, the bulk of the evidence is consistent in showing that new technology is a major determinant in the rise of healthcare costs and expenditure.

It is important to point out that the focus of the analysis here is on the cost of technological change, which is rising health expenditure. The benefits of medical technology improvements – longer life, improved quality of life, prolonged working ability, and so on – are not considered in this literature. Consequently, no conclusions can be drawn on the issue of the net value that patients and society in general derive from innovations.

Since innovation in medical technology and devices is normally associated with rising healthcare expenditure, and despite their proved benefits, the chapter pushes forward in assessing the issues of whether technological innovations in medical devices and in medicine are financially sustainable. Moreover, we explore what kind of policy measures should be enacted to sustain these improvements without constraining the number of beneficiaries and the acquisition and access to significant technologies. The analysis shows that the best way to approach these issues is to frame them into the broader debate on welfare system reforms that EU Member States will need to adopt in the next few years. In particular, this Study is in line with a vast body of literature that suggests a mixture of coordinated policies, often referred to as "triple diversification of the expenditure": i) a rebalancing within the components of public social expenditure, at present too concentrated on pensions; ii) a rebalancing between public and private sources of financing through the adoption of co-payment schemes; iii) a rebalancing within the composition of private social expenditure, in order to strengthen the organised institutional pillars of pension and healthcare funds.

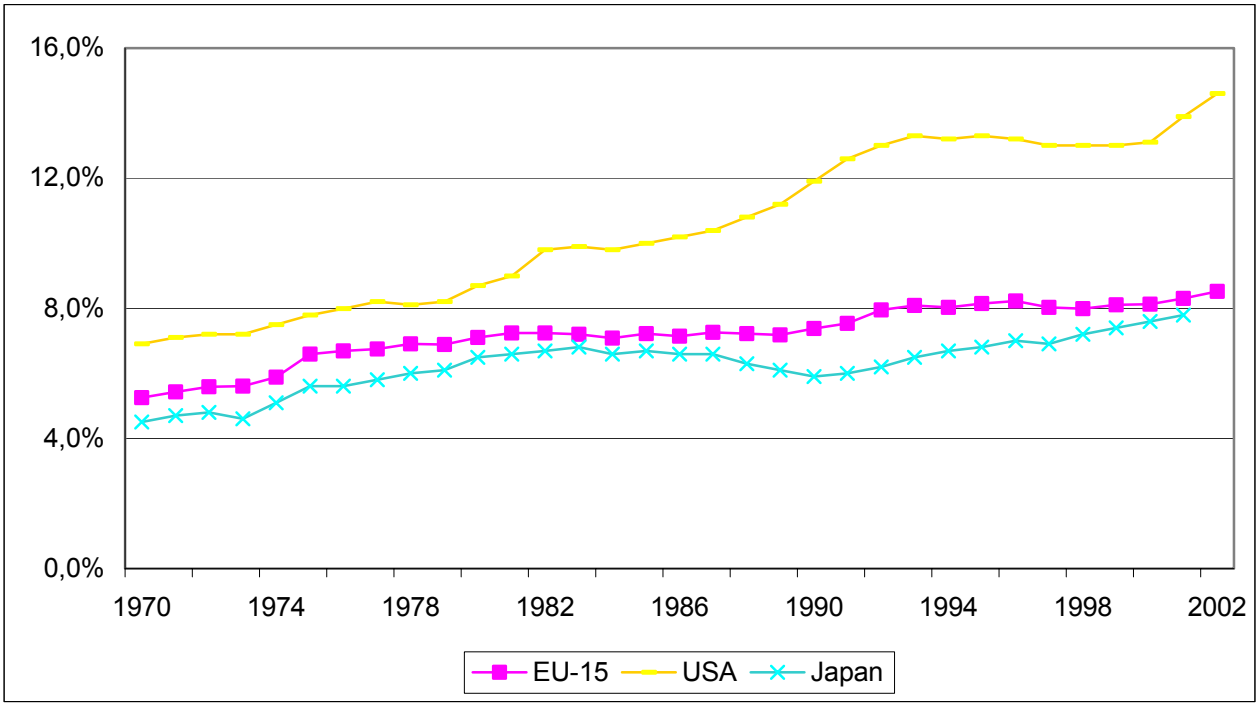
EU Member States appear to have margins to strengthen the diversification of the financing sources for the long-term sustainability of healthcare expenditures. With the appropriate use of market regulation and fiscal incentives and support to the disadvantaged categories of patients, this structural change can take place preserving the fundamental social choices. This could partially loosen budget constraints on health systems as well as the focus on cost-containment, and allow

increasing potential for high price-performance products both in the public and private markets. The industry of medical devices and of high-tech medicine could become one of the investment targets for health funds, and benefit from a significant financial source for R&D and innovation.

3.1 Introduction

Industrialised countries are spending record amounts on healthcare. In 2002, EU-15 and EU-19[8] respectively spent on average 8.5 and 8.1 percent of their GDP on healthcare, both up by 0.4 from 2000, and 1 percentage point from 1990 (figure available only for EU-15). The US is topping this trend, having passed from approximately 7 percent in 1970 to almost 15 percent in 2002[9].

Figure 1. Total health expenditure as a percentage of GDP



Source: OECD Health Data (2004).

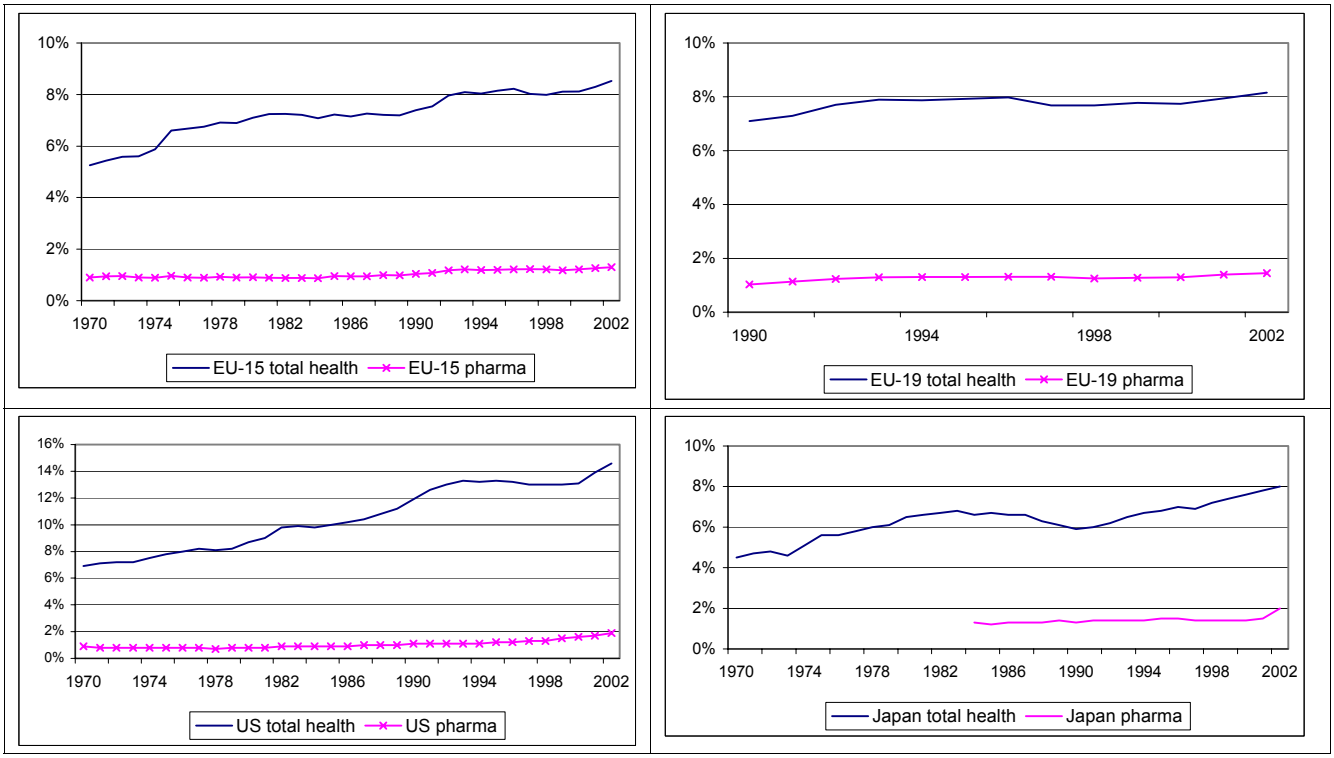
Healthcare spending has out-paced economic growth over the past decades, and not only during the economic downturn spells. Trends in Figure 1 reveal some common patterns for the last decade: the first three years of the period (1990 to 1992) witnessed higher growth of the ratio than the following five years, when governments and insurers in several EU Member States, as well as in the US and Japan, applied cost-containment measures. For the EU and the US, the ratio remained roughly flat between 1993 and 1998 and started to rise again by the end of the 1990s, reflecting deliberate policies in several countries to relieve pressures arising from cost-containment in previous years. From 2001 slow economic growth determines the marked increase in the ratio.

Due to the shortage of reliable long-term series on expenditure on medical devices, it not possible to assess the relationship between trends in health expenditure and medical device expenditure. Figure 2 illustrates the series of total health expenditure and pharmaceutical expenditure (that together with

[8] OECD Health Data 2004 provides figures only for OECD countries, which for the European Union are the EU-15 plus Czech Republic, Hungary, Poland and Slovak Republic ("EU-19").
[9] An extensive analysis of health expenditure trends in OECD Countries can be found in Huber and Orosz (2003).

medical devices constitute the high-tech segment of the aggregate) that present in all cases a positive correlation.

Figure 2. Total health expenditure and pharmaceutical expenditure as percentages of GDP



Source: OECD Health Data (2004).

The pressure on public budgets from accelerated healthcare spending has been a major policy concern in all countries over the past two decades and in particular in the recent years of economic slowdown. Tracking and explaining the growth in medical spending in all national systems is a prominent issue in government, academia and industry research. A body of literature examining the determinants of healthcare expenditure has emerged in an effort to explain why health expenditure has risen so much in all health systems, and also to offer suggestions as to what variables can be influenced to reduce costs. The main driving forces identified by this large body of literature are ageing populations, income growth - which has gradually improved the level of well-being and as a result the demand for health treatments - and technology, which is the focus of the next paragraphs of this chapter.

3.2 The medical technology - health expenditure link: theoretical aspects

Demographics and income growth have been identified as drivers of health expenditure since early studies, both theoretical and empirical. On the contrary, the predictions from economic theory on the impact of innovation in medical technology are not clear-cut, and its relevance has gained wide acceptance only in more recent times[10].

The economic analysis of the interplay between medical technological change and health spending builds upon the basic impact that innovations may spur on demand and supply of medical care. Complexity may then be added to the basic framework in order to include dynamic aspects,

[10] A synthetic but comprehensive review of the determinants of health expenditure growth can be found in Docteur and Oxley (2003).

institutional arrangements and the attitudes of, and incentive structures facing, healthcare policy-makers and insurers, providers and patients.

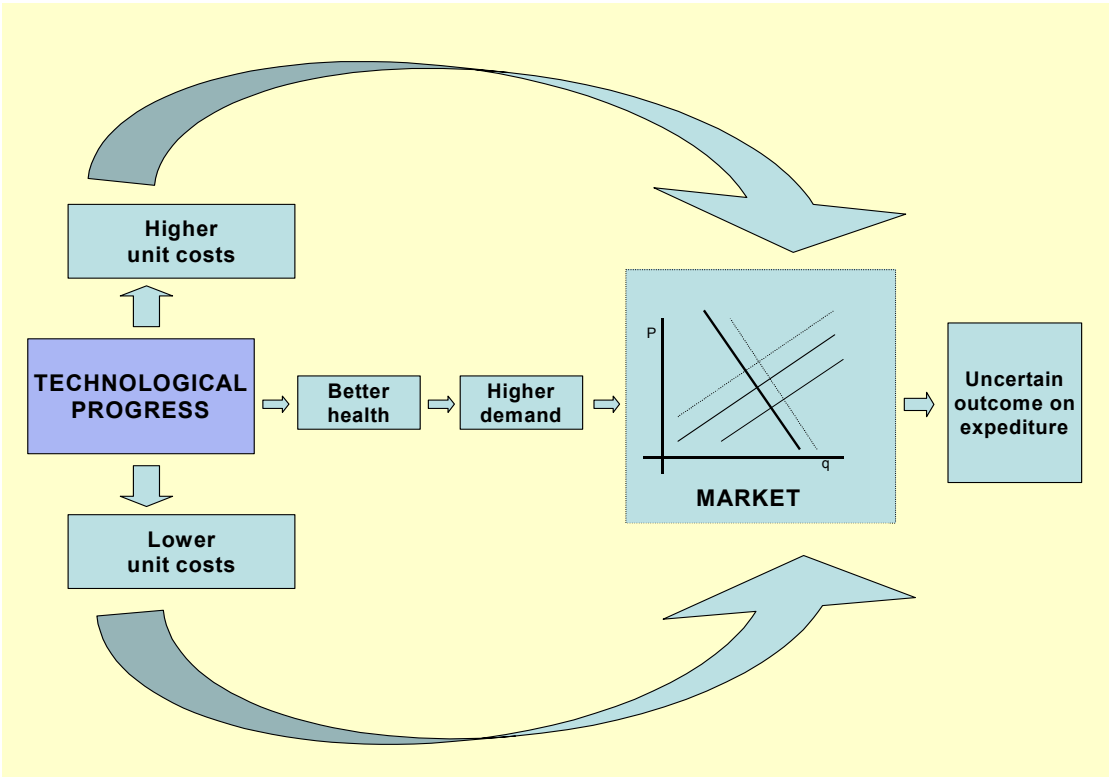
The standard static mechanism (a), and a model of long-run interaction (b), plus its dynamic evolution driven by changing attitudes of policy-makers and insurers (c) will be illustrated in the following.

a. The single period impact

From a static point of view, technological progress can in general be seen as something that lowers the cost of producing an industry's output, and under normal conditions (if the price elasticity of demand is less than one, as it is generally thought to be in the health services industry), total spending should decrease. When new techniques generate a cheaper way of treating health outcomes, there could be expenditure reductions associated with technological change.

However the demand for health services can be thought of as a derived demand, the fundamental commodity that is being valued by consumers (patients and doctors) being "good health" not health services. Therefore, if technical progress takes the form of progress in the ability to transform health services into "good health", rather than reducing the resource cost of producing health services, then the demand curve for health services would shift out, so that total health spending could increase (even if the price elasticity was less than one).

Figure 3. Dynamics of the impact of medical technology change on health expenditure growth



As a consequence, the overall net impact of technological progress on health expenditure in simple static models is not determined *a priori*, being the result of the interplay of factors that may point to opposite effects, namely a) the unit cost reducing versus the cost-increasing effect of the innovations (supply-side effect) and b) the derived impact on demand (demand-side effect).

b. Dynamic interactions with health insurance schemes

As for most other sectors, static microeconomic models are unsuited to policy analysis of the medical and health market: the framework needs to account for dynamic multi-period effects and institutional factors. The fact that all national health systems provide some form of institutional health insurance – public and private – has spurred a stream of theoretical research and modelling on the relationship between technological change and expenditure in health through an "intermediate" dimension, healthcare insurance (Feldstein, 1977; Goddeeris, 1984; Pauly, 1986; Weisbrod 1991). In this framework, new technologies drive up both cost and demand for care (and expenditure), as well as demand for insurance. At the same time, expanding insurance, i.e. those including more people and encompassing more health procedures and products (with higher expenditure), provides increased incentives to the development of new technologies. A by-product of this process is the long-run growth of healthcare expenditure.

It is important to point out that the focus of the present analysis in fact is not on the "traditional" effect of insurance in increasing utilisation of *existing* technologies (see Box 1), rather on the effect of insurance in enhancing the development of *new* technologies.

BOX 1: The relationship between medical insurance and health expenditure

In most national systems, a sizeable portion of all medical expenditure is covered by public (tax-financed and government-administered) or private insurance. The basis of this is the fact that the demand for medical care depends predominantly on a person's state of health, and state of health is stochastic, to a relevant extent. Under these circumstances, insurance against the cost of care is expected to emerge, and has indeed done so, to such an extent that it has become the predominant form of payment for most medical services.

The relationship between medical insurance and health expenditure has received a great deal of theoretical and empirical attention, starting from the milestone contributions of Arrow (1963), Pauly (1968) and Phelps (1973).

Focus of most analyses has been the encouragement, in the presence of insurance and moral hazard, of inefficiently great utilisation. In insurance, moral hazard is defined as the alteration of individual behaviour due to the insurance coverage that affects the expected loss. It can occur because insurance affects either the probability of an event associated with a loss, or the size of the loss (conditional on the occurrence of the event). Applied to the health sector, this means that moral hazard arises when the purchase of health insurance encourages individuals to spend less on preventive medical care and/or induces and individual who has experienced an illness to spend more resources on its treatment. In the presence of moral hazard, insurance that reduces risk will also cause larger expected losses. In the health sector, these losses correspond to the consumption of units of medical care whose value to the consumer is less than their cost, because the insurance coverage reduces the user price below cost. This framework explains the concomitance of health insurance and higher health expenditures.

Under this line of reasoning, as with insurance in health, technological change is, simultaneously, an independent variable – causing changes in the extent of insurance coverage – and a dependent variable – being affected by the incentives provided by the extent of the coverage.

This interactive process can be disentangled following Weisbrod (1991):

I. *Insurance system as the independent variable*; *R&D and technological change as the dependent variable:* the level and the direction of R&D efforts and of technological innovation depend among other things on the expected returns, i.e. on the expected size of the

market (utilisation) and on the expected price, that is determined by the private and public health insurance institutions. Policies and rules of health insurance institutions exert an important influence on which new technologies will be accepted into practice and how they will be used, and in turn on the rate and direction of innovation and R&D efforts. Since insurance removes the financial barriers of patients raising the demand for technology, wider insurance coverage will determine more intense incentives to innovate.

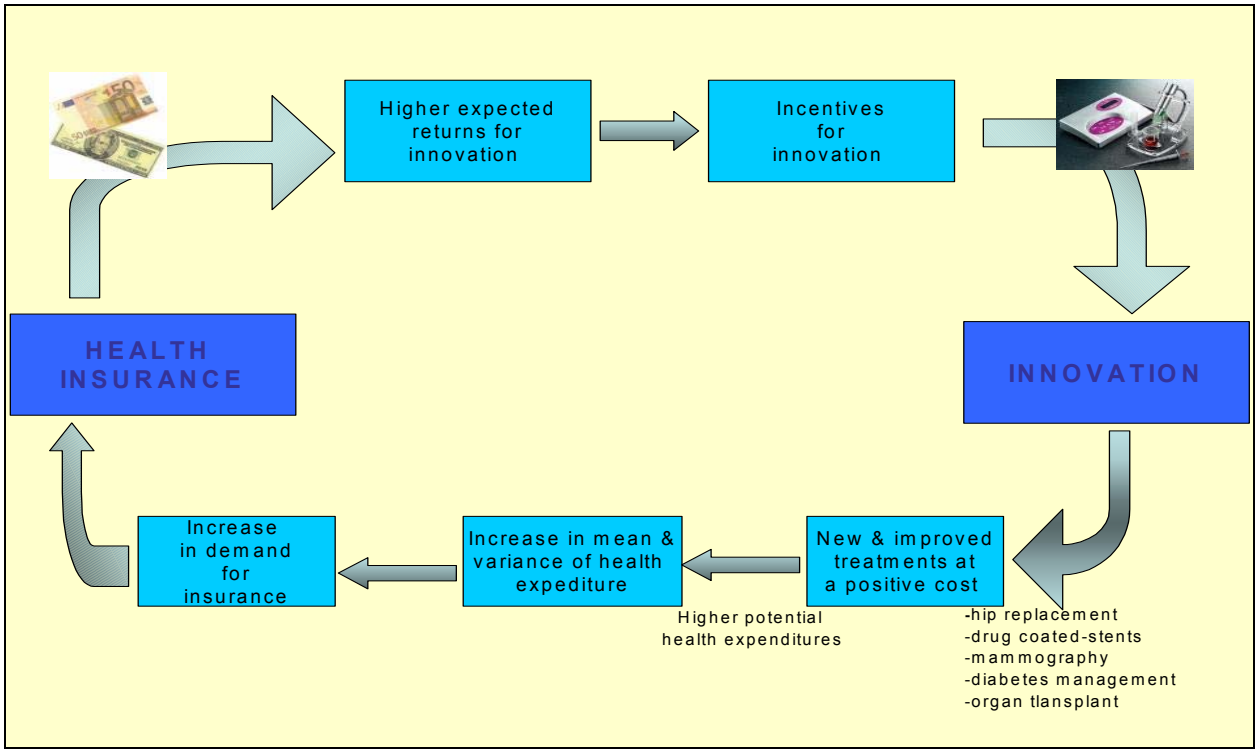
II. *R&D and technological change as the independent variable; insurance system as the dependent variable:* demand for healthcare insurance depends on technological change: if due to innovation a previously untreatable condition becomes treatable at a positive cost, then individuals during their lifetime could encounter an additional unpredictable medical expense for the treatment. This determines an increase in the mean and variance of their expected health expenditures, and thus, under the standard economic hypothesis of behaviour under uncertainty, an increase in demand for insurance. As Weisbrod and LaMay (1999) report: "*..at the close of World War II only nine percent of the US population had any hospital insurance, for the simple reason that medical science could do very little in a hospital. Today, when it is possible to replace a diseased liver, but at a cost of $200,000 or more, the demand for insurance has understandably soared. ..".*

The stochastic properties of health conditions, and the non-homogeneous distribution within a community of the event "bad health conditions"[11], make room for risk pooling. Demand for collective insurance is thus predicted to increase. The nature of the "merit good" of healthcare, due to its role in the preservation of life, will result in political pressures on governments to make the innovation accessible to all the needy population, regardless of the ability to pay. Beside private insurance, also public insurance coverage is then expected to rise.

III. *The growth of healthcare expenditure is a by-product of the self-fulfilling interaction between innovation and insurance* (see Figure 4). New technologies and new treatments increase the risk and magnitude of health expenditure for individuals, and thus drive up demand for public and private health insurance (for expanded insurance coverage that includes not only more people, but also an increasingly wider definition of health assistance). Expanded coverage results also in higher (actual and expected) utilisation of new technologies – since insurance eases financial barriers to demand and utilisation – and thus in incentives to innovation; and so on, iteratively.

[11] Excluding the case of epidemics, now extremely rare in Western Countries, and catastrophes.

Figure 4. Health insurance, innovation and expenditure: the interactive process



c. Insurance policies technology adoption and signals to medical innovation: the evolution of the interactive process

In recent decades, most healthcare systems, public and private, affected by increasing public expenditures, have undergone major reforms and change of policies. Reforms aimed at improving the efficiency of the health systems at the micro level have been introduced by most countries (besides measures such as caps on spending, administered prices and volumes, and shift of costs onto the private sector through increased cost-sharing).

A first area of efficiency-fostering reform within public integrated systems has concerned the budgetary separation of public insurers from healthcare providers (mainly hospitals), and the increased financial autonomy and responsibility of the latter. During the 1980s, OECD countries generally made hospital contracts better attuned to achieving the goals of cost control, efficiency and quality of care, with greater attention paid to the incentives inherent in specific payment methods (Docteur and Oxley, 2003). Most reforms at national level that continued through the 1990s up until now, sought to deal with the ease with which medical providers can pass on costs when consumers pay for medical care through a third party. Under this trend, most systems have seen the move from "retrospective systems" – whereby healthcare providers are paid on the basis of costs incurred – to "prospective systems" – in which the sum paid are exogenous and independent from the costs incurred.

Retrospective payments operated through the insurance system can encourage overuse of medical resources; on the contrary, under prospective payments, where revenues for patients admitted are largely exogenous and fixed, the organisation's financial health depends on its ability to control cost of treatment. This induces healthcare providers to consider the cost consequences of their decisions (Feldstein and Friedman, 1977). The tendency, initiated in both the US public and private health insurance systems in the early 1980s, in subsequent years spread to most healthcare systems. Means of this current of reforms are schemes such as the Diagnosis-Related Groups (DRG) that have had several national applications and variations, but that in all systems consist of fixed reimbursements

to hospitals/providers per diagnosis/treatment (e.g. appendicitis) based on the average cost of the treatment[12].

The economic incentives – that drive circularly the interaction between insurance, R&D and innovation – are not invariant to these. Retrospective pricing sends the following signal to the innovation system: "*develop new technologies that enhance the quality of care, regardless of the effects on costs*". While the new signal sent under perspective systems is: "*develop new technologies that reduce costs, provided that quality does not suffer too much*"[13].

High technology medicine is generally regarded as a source of significant professional prestige, and in general, social values favour its application, especially for life-threatening conditions. Before the tightening of the budgets and the switch to perspective mechanisms and in the presence of generous insurance, as long as new technologies were seen as offering even small health benefits compared with existing practices, these were adopted. Feedback signals were often in terms of shortcomings in efficacy and safety and problems with the ease of operation, not cost reduction.

The growing budget pressures and the switch to perspective payment systems changed the incentives in the system. As a consequence, technology improvements started to be directed not just at enhancing performance but also at reducing costs, of equipment and of treatment (Gelijns and Rosenberg, 1991).

BOX 2: Empirical evidence supporting the dynamic interaction

Several authors have observed that the pattern of technological change in healthcare since World War II is the result of the interplay between health insurance systems and product development, and that it has nourished health-care costs and expenditure (Danzon and Pauly, 2001; Peden and Freeland, 1998 and 1995; Feldstein, 1995;; Weisbrod 1991). Feldstein (1971, 1977) for instance tests empirically a model of the hospital industry and finds that the explosion of hospital costs and expenditures, in the US during 1958-1973, reflects the increase in the demand for hospital care fuelled by technological innovation and sustained by the growth of private and public insurance.

A handful of empirical studies confirm that health insurance schemes have influenced the adoption and the development of a range of high-technology medical services (Russell, 1979; Sloan, Valvona et al. (1986), Gelijns and Rosenberg, 1994; Hill and Wolfe, 1997; Baker and Wheeler, 1998; Cutler and Sheiner, 1998). Russell (1979) for instance finds statistical evidence of faster adoption of electroencephalography and cobalt radiation therapy in US regions where insurance coverage was higher, while Sloan et al. (1986) find evidence that insurance coverage affected the diffusion of some surgical techniques (among which hip arthoplasty, coronary bypass and cataract surgery). In addition several studies have validated the responsiveness of R&D and innovation efforts to specific insurance-related incentives. Gelijns and Rosenberg (1991) report that percutaneous transluminal coronary angioplasty (PTCA) were first granted in the US a reimbursement fee to the healthcare provider that exceeded the cost of the procedure. Together with a rapid adoption of PTCA, this stimulated a high level of incremental innovation in PTCA catheters. Cochlear implants instead were awarded a reimbursement level that covered only part of the intervention; this led not only to their under-diffusion, but also to a marked reduction of R&D investments (Kane and Manoukian, 1989). Following the development of dialysis, the US government in 1972 first enacted legislation to cover the treatment of all end-stage renal disease patients, then decreased the reimbursement rates to control the upsurge in expenditure; in line with the present argument, this stimulated research in cost-reducing directions: Rettig and Levinsky (1991) estimate that as a consequence the equipment and supply (non-labour) component of the total cost per dialysis treatment was reduced from about one-

[12] An accurate description of the evolution of national healthcare policies and their move towards cost-containment and efficiency-enhancing schemes can be found in Docteur and Oxley (2003).
[13] Citations are from Weisbrod (1991).

third to less than one-fifth.

Though more limited, empirical evidence also exists on the influence of improvements in medical technology on the diffusion of health insurance. Thomasson (2002) proves this looking at long-term trends and history of the US system.

Evidence is also abundant on the change of adoption patterns and on the development of new technologies following the switch from retrospective to prospective schemes. Under retrospective systems, broadly speaking prior to the 1980s, even small technological improvements were often adopted by physicians, hospitals and providers, without regard to costs. This framework led to an un-equalled wave of innovation in health technology accompanied by a rocketing expenditure on health. Russell (1979) shows that in the late 1960s and early 1970s an expansion in the adoption by hospitals of medical devices occurred despite a general lack of evidence on the efficacy for a number of these, among which were respiratory therapy and intensive care. The switch from retrospective to prospective systems determined new patterns of utilisation and of innovation in medical technology. Prospective reimbursement affected in a restrictive way the extent and speed of adoption of new technologies in hospitals (Romeo Wagner et al., 1984). Baker (2001) for instance finds that in the US the expansion of managed care during 1983-1993 was associated with slower diffusion and lower availability of MRI.

The new incentives determined more emphasis on cost reduction and less on costly quality improvements, and hence to a new wave of cost-effective and efficiency enhancing innovations (Weisbrod, 1991; Goddeeris, 1987; Gelijns and Rosenberg, 1991). Expensive procedures, such as cholecystectomies, became preferred R&D targets of device manufacturers, aimed at developing a variety of minimally invasive devices. Manufacturers of lithotriptors replaced the expansive X-ray system and short-lived electrode configurations originally embedded in the device with less costly alternatives. Along the same line, the development of percutaneous transluminar coronary angioplasty (PTCA) – safer and less expensive (mainly due to shorter hospitalisation) than surgical bypass – was reinforced by the mid-70s by emerging limitations in the financial capacity of the surgical bypass alternative[14]. When the ceiling for US government payment for kidney dialysis was placed in the 1970s a new generation of dialysers were developed, that cut the time required per session nearly in half (from 6-8 hours to 3,5-4,5 hours) leading to substantial savings in professional labour costs, a major cost component (Weisbrod, 1991).

The direction of the interactive process involving insurance, R&D and innovation is thus increasingly influenced by the change in incentives associated with the tightening of the insurance budget (reflected in the shift from retrospective and cost-based insurance reimbursement, to prospective and exogenous insurance reimbursement). In this industry, for several aspects and reasons that we have shown, insurance has done considerably more than just transfer resources from the "lucky" to the "unlucky". It has shaped the structure and direction of the market itself.

3.3 The medical technology – health expenditure link: review of the empirical literature and of the evidence

Static and dynamic frameworks of analysis illustrated in the previous paragraphs provide mixed indications on the medical technology – health expenditure link: the effect of cost-reducing technologies, increasingly incentivised by constrained health insurers, could in principle offset the demand-side effect and the self-fulfilling interaction. It is then necessary to switch to empirical analysis in order to collect evidence on the dynamics highlighted above, and on the sign of the link.

[14] Later studies revealed smaller cost differences between the two procedures, partly because the initial analyses had not incorporated the cost of dealing with restenosis that is associated with PTCA, see the case-study on drug eluting stents in Chapter 4.

Starting from the 1990s, an increasing number of studies have included technological change in healthcare among the key drivers of health expenditure growth, beside "traditional" factors such as income growth, aging and demographic changes[15].

The empirical assessment of the impact of technological progress on healthcare expenditure is not straightforward, for several reasons, the main two being the complexity of:

1. representing and measuring technological change;
2. identifying and measuring all the dimensions, direct and indirect, of the impact of a technology.

Technology in healthcare can be defined as the stock of usable knowledge regarding healthcare treatment, that is incorporated in drugs, devices and medical and surgical procedures used in medical care as in the organisational and supportive systems within which such care is delivered. Applied more narrowly to medical devices, this reference definition covers not only innovation in the *products/devices*, but also in the *processes* for their use (new surgical procedures), as well as in the *skills* and *support systems* through which they are operated and dispensed. In this large connotation, technology cannot be measurable or quantifiable, and proxies need to be sought out and selected. Several proxies have been adopted in the literature - such as indicators reflecting the stock and usage of the devices, R&D indicators (R&D expenditure or number of dedicated employees), patents, time indexes (since technological change occurs over time) – but all of them present some limits, as reviewed in Kleinknecht et al. (2002).

Also the identification and measurement of all the dynamics, direct and indirect, generated by a technological innovation is a complex task. In many cases just the assessment and measurement of the direct costs of a technology may present methodological and practical difficulties. For a capital-embodied technology for instance, direct costs are substantially broader than the mere purchasing cost of the device, and include the cost of the space, of the supervisory personnel, training, maintenance, supplies, and so on.

BOX 3: The technology-expenditure link: beyond income growth and demographics

Medical technology as a factor in explaining health expenditure trends is still neglected by a number of relevant studies and exercises on the issue. Despite the increasing evidence that technology is an important force driving health spending, as is argued in this chapter, difficulty in defining and measuring health technologies is cited as the primary reason for the lack of consideration. This omission, as it will be shown here, may determine significant biases in the outcome of the empirical work on the subject.

Pammolli and Salerno (2004) have assessed the potential under-estimation in the long-term projections of healthcare expenditure on GDP performed by the Ecofin (Ageing Working Group of the Economic Policy Committee of Ecofin, the Council of Economics and Finance Ministers of the European Union), that have included only demographics and income growth as driving factors.

The Ageing Working Group (AWG) has been created within the Economic Policy Committee of Ecofin with the mandate of developing, for all Member States, long term projections of the principal budget items affected by population aging, such as healthcare, pensions, education and unemployment allowances (European Union Economic Policy Committee, 2001 and 2003). These projections are assuming greater importance as instruments to assess future budget constraints and adequate supply of benefits and services. Projected health expenditure is mainly driven by income growth and demographic factors. In

[15] A complete review of the methodologies and main results of the empirical literature on health expenditure determinants is in Gerdtham and Jonsson (2002).

particular per capita public healthcare expenditure (PHE) is assumed to grow at the same rate of per capita GDP. In the base year and for each age bracket, AWG calculates the value of per capita PHE; then, this value is projected under income growth estimates and demographic extrapolations.

In order to assess this methodology and its results, Pammolli and Salerno test backwards the hypothesis of identity of growth in per capita GDP and per capita PHE. Their analysis shows that on average the growth rate of per capita PHE has been higher than that for per capita GDP, by approximately one percentage point. The hypothesis at the base of the AWG projections, according to their calculations, is thus not empirically confirmed.

Building upon this finding, they perform a simple sensitivity exercise. Starting from the AWG projections of the ratio between per capita PHE and per capita GPD, for each Member State the average compound annual rate of growth of the ratio over the 2050-horizon is first calculated, then is augmented by 0.5-1.0 percentage points to account for the discrepancy found above.

This sensitivity analysis enlarges the projection set to include other driving factors of health expenditure. Technological enhancements and investments in medical devices are surely part of these "residuals".

The results show the AWG projected health expenditure-GDP ratio at 2050 (column a) becomes significantly higher when the projections are augmented by 0.5 (column b) and 1.0 (column c) percentage points to account for the "other factors". In particular the incidence of healthcare expenditure on GDP would be higher by 2 and 5-6 percentage points when, respectively, the rate of growth is augmented by 0.5 and 1.0 percentage points.

Limiting the projection set of health expenditure on GDP to demographics and income growth may lead to a significant under-estimation of this ratio.

Incidence of healthcare expenditure on GDP (percent)

		Projections at 2050				
	Base year 2000	AWG (a)	+0,5% (b)	+1,0% (c)	Difference under +0,5% (d)	Difference under +1,0% (e)
Austria	5.8	8.5	10.9	13.9	2.4	5.4
Belgium	6.1	8.1	10.4	13.3	2.3	5.2
Denmark	8.1	10.7	13.7	17.5	3.0	6.8
Finland	6.2	9.0	11.5	14.7	2.5	5.7
France	6.9	8.5	10.9	14.0	2.4	5.5
Italy	5.5	7.4	9.5	12.1	2.1	4.7
Netherlands	7.2	10.3	13.2	16.9	2.9	6.6
Sweden	8.8	11.8	15.1	19.4	3.3	7.6
UK	6.3	8.2	10.5	13.5	2.3	5.3
Average	6.8	9.4	11.7	15.0	2.3	5.6

Source: Pammolli and Salerno (2004).

The empirical studies have approached the assessment of the connection between technology and rising healthcare expenditures with different methodologies, summarised in Table 1.

Some studies have used a "determinants approach", where healthcare expenditure is econometrically regressed (or co-integrated) on variables that are believed to affect its growth, such as income or demographics, plus variables representing technological progress. Some others have employed the so-called "residual approach". This first evaluates or estimates the impact of more easily identifiable factors, such as rising incomes and changing demographics; then it attributes the portion of health spending not accounted for to technological change. Other researchers have identified specific diseases and technologies and have attempted clinically meaningful measures of the role that technology plays in healthcare cost growth.

All of the different approaches present advantages and limits. Since technological progress is not measurable, the determinants approach requires measurable proxies, which might be imperfect substitutes. On the other hand, the residual approach leaves some authors with perplexities (Neumann and Weinstein, 1991; Gelijns and Rosenberg, 1994; Goldsmith, 1994), since, among other things, it does not pinpoint the precise cause of increases and, most importantly, the reliability of any estimates derived as a residual depends upon the confidence that all other factors and their interaction effects have been fully captured. Case studies, however illuminating, have the methodological problem of sampling and of generalisation from them (Rettig, 1994).

Table 1. Main methodologies of study of the impact of medical technological change on health expenditure

Methodology	Advantages	Limits
Econometric analysis of determinants, including technological change of health expenditure.	Rigorous assessment of significance and magnitude of impact.	Need to represent technological change through measurable proxies that might alter its representation.
Residual approach: estimation of the impact on health expenditure of easily identifiable factors (income, demographics) and residual attribution of unexplained expenditure growth to technological change.	Incorporation of technological change in full (no limitation in representation as in case studies or use of proxies).	No identification of the effect of single technology components; impact of technology overestimated in the likely event of mis-specification of all other determinants.
Descriptive analysis of data and/or facts and evidence from them.	Potential for analysis of relevant relationships not assessable through other methodologies.	Risk of identifying spurious relationships. Non-rigorous assessment of quantification and direction of the relationship.
Case studies on cost of specific technologies and procedures over time.	Potential for rigorous assessment of impact on costs and expenditure for single technologies.	Sampling bias. Difficulty in generalisation of results.
Case studies on cost of specific diseases and conditions over time.	Potential for rigorous assessment of impact on costs and expenditures associated to single diseases.	Sampling bias. Difficulty in generalisation of results.
Surveys and interviews with experts in the field.	Potential for synthetic representation of processes and effects, through the view of experts.	Individual view bias.

Economic and medical literature has been extensively researched for studies that have addressed the issue of the relationship between medical technological change and health expenditure growth. Healthcare and economic databases (MEDLINE, EconLit) were searched using keywords such as health expenditure or health cost plus technology, technological change, productivity, innovation. Bibliographies of retrieved articles were screened to identify additional publications. In addition the following journals have been hand-searched for articles on the matter, published from year 1990 to October 2004:

- American Economic Review
- American Journal of Public Health
- European Economic Review
- Health Affairs
- Health Economics
- Health Care Financing Review
- Health Care Management Review
- Int. Journal of Health Planning and Management
- Journal of the American Medical Association
- Journal of Econometrics
- Journal of Economic Perspectives
- Journal of Health Economics
- Journal of Human Resources
- Journal of Public Economics
- Medical Care
- Medical Care Research and Review
- New England Journal of Medicine
- Quarterly Review of Economics and Finance
- Quarterly Journal of Economics
- The Lancet

Relevant studies found through this search are synthetically reviewed in Table 2.

Table 2. Analysis and assessments of the impact of technological innovation medical technology and medical devices on health expenditure

Author	Typology of work and analysis	Findings
Bentkover, Stewart, Ignaszewski et al. (2003)	Estimation through an economic model of the potential savings that could result from the introduction of new technogies such as cardiac resynchronisation therapy for class III/IV hearth failure patients (in Canada).	Potential savings in Canada for this group of patients could **reduce the total annual costs by approximately 10%**.
Binder, Schiel, Binder et al. (1998)	Analysis of clinical outcome and associated costs of a sample of patients with haematologic malignancies undergoing antibiotic regimen.	Significant dependence of clinical outcome on aminoglycoside peak concentrations, detectable through in vitro diagnostics (drug therapy monitoring), that allow dosage adjustment. Considerable cost savings result with the application of drug therapy monitoring (costs for patients with low aminoglycoside peak concentrations were 1.8 times higher than for patients with adequate concentrations).
Blomqvist and Carter (1997)	Econometric analysis of time series on national health expenditure for 18 countries. Inclusion in the model of a linear trend to account for technological change.	Real expenditure on healthcare grows by roughly 2% per year, net of the impact of determinants such as income growth. **This independent time trend is interpreted as being principally due to technological progress**.
Bradley and Kominsky (1992)	Analysis of inpatient costs and utilisation patterns for a large sample of US hospitals (1984-1987).	**Technology-related factors accounted for approximately one-third of the real increase in costs**.
Braunschweig (2000)	Analysis of heart failure-related hospital days associated with cardiac resynchronisation in patients with severe heart failure and delayed intraventricular conduction.	**The need for hospital care decreased significantly after cardiac resynchronisation**. The total number of hospital days was reduced by 82%.

Author	Typology of work and analysis	Findings
Bryan, Buxton and Brenna (2000)	Analysis of changes in running costs and direct observation of resource use in a UK hospital following the introduction, in 1995, of a computer technology system in radiology (picture archiving and communication systems - PACS).	**PACS has added to hospital running costs by approximately 1.8%.** Net additions to overall costs crowded out the expected efficiency and cost gains. Key additional cost sources include maintenance of the PACS technology, dedicated onsite maintenance staff. Among the savings: reduced expenditure on film and chemicals, clinician time. No significant reduction in average length of hospitalisation.
Chernew, Hirth, Sonnad (1998)	Extensive review of the literature on the impact on new medical technology on cost growth.	*"…**Medical technology appears to be a prime driver of healthcare costs**…".*
Cromwell and Butrica (1995)	Descriptive analysis of cost components for a large database of US hospitals (1980-92).	The dramatic growth in the operating room, catheter lab, **and other technologically driven cost centres is accompanied by a growth in hospital costs** for the period of investigation, well in excess of inflation.
Curnis (2003)	Analysis of hospital costs and clinical effectiveness of cardiac resynchronisation in heart failure.	In the 12 months following the implant, **overall costs were reduced by 24%**. Cardiac resynchronisation in heart failure patients represents an efficient approach in the hospital perspective and allows a less intensive use of clinical resources.
Cutler, McClellan and Newhouse (1999)	Analysis and estimation of cost trends (based on various data sources and literature review) for the treatment of hearth attack (US, 1984-1991).	**The cost of heart attacks has increased by 50% in real terms between 1984 and 1991, due to more intense surgical therapies** such as cardiac catheterisation, bypass surgery, angioplasty. (When also benefits are taken into account the value of improved health is greater than the increased cost).
Cutler and Huckman (2003)	Quantitative and econometric analysis of the long-term diffusion of PTCA – a treatment for coronary artery disease – and of its impact on cost of care; data 1980-2000, for New York State.	**Growth in the use of PTCA led to higher costs, despite its lower unit cost compared to CABG**, the previously dominant procedure. In particular the growth of PTCA in the 1980s occurred through treatment expansion and was accompanied by little offset in the use of CABG and thus by large increases in the overall cost of care. By the 90s however improved PTCA became a substitute for more expansive CABG, thus leading to an offset of the cost increases.

Author	Typology of work and analysis	Findings
Dahler-Eriksen, Lauritzen, Lassen et al. (1999)	Assessment of costs and savings associated with a trial (in Denmark, year 1996) where a sample of general practitioners were allowed to measure C-reactive protein (CRP; test for the diagnosis and follow-up of infectious diseases) using a point-of-care test (as an alternative to sending blood samples to hospital laboratory).	The savings from decreased hospital laboratory testing resulted higher than the increased costs for the point-of-careCRP test.
Di Matteo (2005)	Econometric analysis of the impact of age distribution, income and time, the latter as a proxy for technological change; data for US States (1980-1998) and Canadian Provinces (1975-2000).	Time accounts for about two-thirds of health expenditure increases. Thus **technological change explains the bulk of health expenditure increases (if one accepts that time is a good proxy for technological change)**.
Feldstein (1977)	Econometric analysis of the determinants of the increase of hospital costs over the period 1955-1975 for the US.	Hospital costs have risen sharply because insurance has increased the demand for hospital care. Hospitals have responded to this increased demand by raising their prices and providing more expensive technology-intense quality of care. **Medical technologies have significantly contributed to increased hospital expenditures and costs through this "induced" effect**.
Feldstein (1995)	Author's perspective.	**The rising cost of hospital care** – leading component of health expenditure in all systems – **has been driven by changes in medical technology** and style/quality of care (more inputs per patient day rather than higher prices for given inputs).
Fuchs (1996)	Survey: descriptive analysis of responses from questionnaire sent to health economists and practicing physicians.	81% of health economists and 68% of practicing physicians **gave a positive response to the question: "*the primary reason for the increase in the health sector's share of GDP over the past 30 years is technological change in medicine***".
Fuchs (1999)	Descriptive analysis of level of utilisation of seven frequently used procedures based on medical devices for the US, 1987-1995.	The median rate of increase in utilisation was 11.1% per year. No substitution effect was noted between alternative technologies (CABG and angioplasty): **increase in utilisation, though associated to cost-effective technologies, is a major expenditure driver**.
Ginsburg (2004)	Author's perspective.	*"..Over the long term,* ***new medical technology has been the dominant driver of increases in healthcare costs*** *and insurance premiums. .."*.

Author	Typology of work and analysis	Findings
Ginzberg (1990)	Author's perspective.	**"**…***High-tech medicine is responsible for the severe cost escalation of the US medical care system***…"**.**
Goetghebeur, Forrest and Hay (2003)	Extensive review of studies on the determinants of healthcare costs.	**A number of peer-reviewed studies report that new technology is a major determinant in the rise of healthcare expenditures**; and although new technology exerts both upward and downward pressures on healthcare spending, overall new technology is estimated to represent 22% of the increase in healthcare spending between 2001 and 2002.
Hay (2003)	Regression analysis of determinants of inpatient expenditures at State-level for the US (1998-2001).	During 1998-2001 inpatient expenditure per member increased by an average of 5.9% annually**. Hospital technology** (proxied by variables such as percentage of hospitals with high-tech equipment) **accounted for 19% of the increase and medical wages (reflecting in part higher skills necessary to operate new technologies) for 20%**.
Heymann, Brewer and Ettling (1997)	Estimation of clinical and economic benefits associated to new (in vitro) diagnostic techniques, that on average reduce of two weeks the time to culture and identify tuberculosis.	The reduction in cost of treatment of tuberculosis is estimated at 18%.
Holahan, Dor and Zuckerman (1990)	Descriptive and regression analysis of changes in Medicare expenditures for physician services per enrolee. (US, 1987-1992).	**Cost growth was greater in specialties likely to have experienced greater technical innovation**.
Ikegami and Creighton Campbell (2004)	Decomposition of changes in national medical expenditure for Japan (1980-2002).	For nearly every year in the period, **spending attributable to technology grew at a rate lower than that of GDP growth**. This finding for Japan – where strong pricing control measures on medical devices have been put into effect – lead the authors to conclude that "… evidently the key impact on spending is not technology itself but how it is priced…".
Katz, Welch and Verrilli (1997)	Analysis of expenditure across different clinical categories for physician services (to the elderly) in US and Canada (1987-1992) on micro (claims) data.	**Cost growth was greatest for more technologically intensive clinical categories**.

Author	Typology of work and analysis	Findings
Koenig, Siegel, Dobson et al. (2003)	Regression analysis on state-level physician cost data for the US (1990-2000).	Over the investigated period, nominal physician expenditure per capita grew 4.7% annually. **11% of this growth is attributed to technology**, proxied mainly by percentage of beds offering technology intensive care (while 42% is attributed to general price inflation and 17% to general economic variables and demographics).
Meara, White and Cutler (2004)	Regression analysis on household expenditure for health in the US (1963; 1970; 1977; 1987; 2000); literature review and authors' view.	Population aging (focus of the study) accounts for only a small part of medical spending growth since 1970. **The major driver of spending growth is technological change**.
Murphy (1998)	Estimation of cost changes determined by the three major technology increases over time in the diagnosis and treatment of peptic ulceration (on cost data for the UK).	The first two innovative phases generated increases in costs; the third has substantially decreased the cost of treatment. **The evidence from this study is insufficient to support the assertion that new technology in general leads to either an increase or to a decrease in healthcare costs**.
Newhouse (1992)	Descriptive analysis of figures and data for the US (1950-1989), based on the residual approach.	Traditional factors – aging population, income growth, spread of insurance, physician-induced demand – can explain only less than one quarter of the recorded increased in health expenditure. **The residual increase is attributable to technological change**, as also confirmed by some data shown.
Okunade and Murthy (2002)	Regression analysis – for the US, 1960-1997 - of the relationship between health expenditure, income growth and technological change, proxied by health R&D expenditure.	**Changes in R&D spending, as a proxy for changes in technology, is a statistically significant long-run driver of the rising healthcare expenditur**e.
Pammolli and Salerno (2004)	Projection at 2050 of healthcare expenditure/GDP for EU Countries based on the extrapolation of past trends, and assessment of the discrepancy (residual) with the same projections based only on demographic changes and income growth.	Health care expenditure/GDP ratio projected from past trends is 2-5.5% higher than that projected on the basis of income and demographics evolution only. Since past trends include, beside demographics and income changes, also changes in medical technology, **the discrepancy (residual) can be interpreted as the significant projected impact of changes in medical technology**.
Peden and Freeland (1995)	Regression analysis (US National Health Accounts, 1960-1993) on the determinants of medical spending growth. Technological progress proxied by non-commercial medical research.	Non-commercial medical R&D spending generates about 1/4 of the 1960-1993 real per capita medical spending and 1/7 of that for 1983-1993. Since in the model growth in technology is greater when insurance coverage is wider, **the set of variables that represent technical progress (R&D plus insurance coverage level) account for about 70% of the growth over the period.**

Author	Typology of work and analysis	Findings
Peden and Freeland (1998)	Regression analysis (US National Health Accounts, 1960-1993) on the determinants of medical spending growth. Technological progress is modelled as a function of insurance coverage and of R&D.	**About two-thirds of 1960-1993 spending growth came via cost-increasing advances in medical technology** resulted from commercial R&D induced by coverage levels and non commercial medical research.
PriceWaterhouseCooper (2002)	Review of the literature, analysis of costs of healthcare providers, interviews with experts.	**Medical advances** (defined as drugs, medical devices, treatments and testing) **result as the major driver of healthcare costs, explaining 22%of the increase**.
Reinhard (2003)	Survey of studies on the US on the impact of aging of the population on health costs.	Most of the annual growth in national health spending has not been driven by the aging effect (focus of the analysis), rather **than other factors that include new medical technology** (together with rising per capita incomes, workforce shortages).
Rettig (1994)	Review of the literature; author's view.	There is a **general consensus that a significant share of annual real healthcare cost growth is attributable to medical technology**.
Schumacher and Barr (1998)	Review of clinical and economic studies pertaining to the use of therapeutic drug monitoring (TDM; through in vitro diagnostics).	The studies that examined economic variables show TDM-influenced changes in therapies that resulted in significant savings in cost of care (and the few studies on cost-benefit analysis showed that TDM yielded a range from 4:1 to 52:1 in benefit-to-cost ratio).
Schwartz (1987)	Residual approach (assessment on the impact of non-technology causes of cost growth and attribution of the unexplained residual to technology).	**Medical innovation is the primary factor contributing to the upward trend in healthcare expenditures.**
Scitovski (1985)	Analysis of changes of treatment patterns for selected illnesses for a hospital (1971-1981, California-US).	**Breakthrough technologies** (such as intensive care units, radiation therapy and chemotherapy and coronary bypass surgery) **were found responsible for cost growth**.
Shactman, Altman, Eilat et al. (2003)	Extrapolation of current (at 2003) trends in hospital spending to 2012 for the US. Decomposition of the projected increase and attribution to medical technology of the unexplained residual.	Of the 4.8% annual real growth rate in hospital spending, 28% is attributable to demographics, 29% to the excess of hospital inflation over the amount of inflation in the general economy and **the remaining 43% represents the use of new technologies**.

Author	Typology of work and analysis	Findings
Shapiro, Shapiro and Wilcox (2001)	Long-term (1960s -1990s) analysis of input and resources required for cataract surgery.	The technique for extracting cataracts has improved substantially over the past 30 years, leading to a dramatic decrease in the resources required (length of hospital stay, surgeon/physician time, no need of post-operative spectacles and contact lenses). Even without accounting for quality improvements, **the real cost of cataracts over time fell by a substantial amount**.
United States Congress Office of Technology Assessment (1984)	Descriptive analysis and cost decomposition of data on hospital costs in the US and medical activity (1970s and beginning of 80s).	*"US healthcare costs have escalated rapidly over the past 15 years, and **medical technology is the primary cause of the increase**".*
United States General Accounting Office (1992)	Descriptive and regression analysis of hospitals' cost structure, US (1980's).	Real hospital operating costs increased in the US by 63% during the 1980s. Descriptive analysis of hospital cost determinants and regression analysis (on cost structure changes) show that "***the measured rise in costs largely results from innovations in medical technology intended to improve patient care***".
Wilensky (1990)	Author's perspective.	*"…**Medical technology has been responsible for rising medical care expenditures** (as well as for improving health status and increasing life expectancy)…".*
Zweifel, Felder and Meiers (1999)	Regression analysis of healthcare expenditure determinants, on patient data from two Swiss sick funds (1983-1994). Technological change proxied by a time trend.	"*In 1992, real healthcare expenditure for patients **was 2.1 times higher than in the benchmark year 1981, likely reflecting technological change in medicine***".

The literature review shows that although single new technologies may exert both upward and downward pressures on health costs and spending, the bulk of the empirical evidence is consistent in showing that a new technology is a major determinant in the rise of healthcare costs and expenditure.

In a comprehensive survey of health economists and practicing physicians conducted by Fuchs (1996), 81 percent of health economists and 68 percent of the practicing physicians responded positive to the question "*the primary reason for the increase in the health sector's share of GDP over the past 30 years is technological change in medicine*". And this answer was given despite evidence showing the cost-reducing effect of some single technologies, as for instance in Curnis (2003), Bentkoven et al. (2003), Braunschweig (2000). In particular, a sizeable chunk of medical literature points to the cost-reducing effects of in vitro diagnostic tools and procedures that have proved to allow earlier treatment, to reduce costs of treatment of complications, and can reduce the spread of infectious diseases in the community (Dahler-Eriksen et al., 1999; Binder et al., 1998; Schumacher and Barr, 1998; Heymann et al. 1997). But the overall impact appears positive and significant, ranging from 20 percent (Goetghebeur et al., 2003; PriceWaterhouseCoopers, 2002) to 70 percent (Peden and Freeland, 1995; Newhouse 1992), and averaging some 50 percent. Chapter 5 will provide some explanations that bridge the apparently contrasting findings of decreasing unit costs and increasing overall costs and expenditure.

A large bulk of the evidence reviewed refers to hospital costs, which are adopting sophisticated technologies that have higher fixed and running costs, in order to accommodate patients demand, physician pressures and remain yet competitive (GAO, 1992; Cromwell and Butrica, 1995; Feldstein, 1995). X-ray machines are being replaced with computed tomography (CT) and magnetic resonance machines (MRI) and then by positron emission tomography imaging machines (PET) (Goetghebeur et al., 2003). In the US, the number of imaging procedures has been growing by 8-9 percent in recent years driven by the use of the more sophisticated and costly technologies, CT, MRI and PET (PriceWaterhouseCoopers, 2002). Technology that introduces computer-based information networks for imaging archiving (PACS), are reported to increase annual hospital costs by 1.8 percent (Bryan et al., 2000). New technologies produce impact on hospital costs also through the increase in medical wages, reflecting the higher skills necessary to operate new technology (Hay, 2003).

Some studies have examined growth in physician expenditure. The two studies of this kind reviewed here (Katz, Welch and Verrilli, 1997; Holahan, Dor and Zuckerman, 1990) disaggregate the growth of expenditures by physician type and conclude both that cost growth was greatest in areas where technological change had been higher, such as cardiology, gastroenterology, orthopaedics.

It is important to point out that the focus of the analysis here has been on the impact of technological change on health costs and expenditure; in other words, on the cost of technological change, which is, as we have seen, raising health expenditure. The side of the benefits of medical technology improvements – longer life, improved quality of life, prolonged working ability, and so on – is not considered in this literature. Consequently, no conclusions can be drawn on the issue of the value (or net value) that patients and society in general derive from innovations.

This analysis has confirmed that technological change has accounted for a large part of medical care cost and expenditure increases over time. But, as Cutler and McClellan (2001) point out, "*it does not necessarily follow that technological change is therefore bad. Costs of*

technology need to be compared with benefits before welfare statements can be made. Technological change is bad only if the cost increases are greater than the benefits". The critical policy questions are thus whether the benefits of such expenditure outweigh the costs and whether or not cost-benefit ratios can be improved.

Chapter 4 will present a number of case-studies where such cost-benefit comparisons will be performed. But, as it will be pointed out there, despite the growing body of empirical work, summary conclusions on the net value and cost-effectiveness of technological change in medicine, cannot be drawn. In fact, net value and cost-effectiveness assessments need to be performed on a case-by-case basis (single technology of single condition), and the findings are difficult to generalise.

As for the analysis here, we can conclude that the cost of technological change – rising health expenditure – is now well understood, if not well measured.

3.4 From cost-decreasing innovations to health expenditure increases: bridging the divide

Despite the fact that in the two past decades several innovations have proved cost-decreasing per treatment, medical technology has not proved cost-decreasing in the aggregate, and instead, as seen in the review, has generated expenditure-increasing patterns on an overall level. This paragraph elaborates on this missing link, showing medical and economic mechanisms, as well as empirical evidence, that can help in explaining how innovations, often cost-decreasing in themselves might generate patterns that are cost and expenditure-increasing in the aggregate. Explanatory mechanisms have been identified in a) the increasing indications and applications of the innovations; b) the growing area of treatable conditions, whereby before the innovation some patients just went untreated; c) the increasing use of technologies for the same conditions, especially when they cause less discomfort to patients; d) the broadening definition of diseases; e) the life-extending effect of new technologies, for which each patient bears (or causes) "more years of yearly expenditures".

a. Increasing applications and indications

Several new medical technologies, thought to be cost-reducing per patient treatment, have turned out to be expenditure-increasing in the aggregate due to their application to a wider set of indications and uses than originally anticipated. When the medical practice acquires a new technology and the skills to use it, it is able to shape these technologies further to expand their applications. The initial application of all imaging diagnostics (X-ray, ultrasound, computed tomography and magnetic resonance) was initially targeted to specific organs and functions; their application has since then extended to almost every organ of the human body (Blume, 1992).

b. Growing area of treatable conditions

Several advances have created clinical ability to treat previously untreatable acute conditions. Organ transplant technology is an example of this. Before the establishment of this procedure, a person with serious liver malfunction simply died; now, with a total cost estimated at US$100,000 – 300,000 (National Kidney Foundation, 2005; Taylor at al., 2002) patients can undergo liver transplants. Other examples come from the cardiovascular field: the introduction of the coronary artery bypass graft allowed the treatment of acute conditions that previously went untreated or under-treated (Rettig, 1994); PTCA for instance was not originally applicable to patients with advanced and unstable medical conditions, but as result of refinement in PTCA catheters, the procedure was then applied to more complicated cases (Gelijns and Rosenberg, 1991).

c. Increasing rate of use for the same conditions

Several new technologies that for instance allow lower costs per unit, or cause less discomfort to patients, have decreased the threshold for performing procedures, and induced higher rates of use, a phenomenon sometimes addressed as *treatment expansion* (Cutler and McClellan, 2001). Often new procedures that allow lower unit costs, reduced hospital stays and complication rates than the traditional procedures they replace, have the potential for significant cost savings. But the lower morbidity, risks and discomfort associated with these techniques may lead to increased provision of services to persons who, without the new technology, would have not undergone surgery. Therefore when the cost savings per case are

offset by the increased number of procedures, these techniques will lead to increased costs in the aggregate.

Minimally invasive procedures – for example various types of endoscopic surgery in which access to the body is gained via incisions that are much smaller than those required by traditional techniques – allow the accomplishment of the same objectives as traditional techniques, but with much less morbidity. Several studies have shown that the introduction of minimally invasive techniques has led in many cases to an increase in the total number of procedures performed to patients. The evidence is particularly striking for procedures such as laparoscopic cholecystectomy, where for instance Chernew et al (1997) find for the US an increase of 20-30 percent (depending on the State) in cholecystectomy rates following the introduction, and rapid diffusion, of laparoscopic techniques at the beginning of the 90s; and for a large HMO, Legorreta et al (1993) found that the number of gallbladder removals increased by no less than 60 percent. Thus, although laparoscopic cholecystectomies reduce unit costs by 25 percent (mostly because of shorter hospital stays), their introduction has resulted in an increase, not a decrease, in aggregate expenditure (Gelijns and Rosenberg, 1991). Knee surgery is another example of this pattern, whereby the introduction of arthroscopic techniques have lead to a dramatic increase in the number of people treated so that total expenditures for treating knee problems in the US rose even though the cost of treating each case fell (Weisbrod and LaMay, 1999). Shapiro et al. (2003), illustrate the large increase in the rate of cataract extraction associated to the decrease in its cost and in the related risks and discomfort to patients.

Cutler and McClellan (2001) assess another interesting case of treatment expansion, the introduction of percutaneous transluminal coronary angioplasty (PTCA) in the late 1970s. This new technology provided an intermediate treatment with costs and intensity between those of the existing surgery technique on the one side – coronary artery bypass graft (CABG) – and of the medical treatment for patients with milder coronary artery disease (CAD). Treatment expansion, that occurred among those previously under medical treatment and that underwent PTCA, was large and led to significant increases in the cost of care for CAD; treatment substitution effects, that involved some patients receiving PTCA rather than CAD, were initially offset by treatment expansion. In general, due to the rapid evolution of the technology used for angioplasty, its use has increased dramatically in recent years. In 1998 in the US, the number of procedures performed for elderly patients was nearly four times that in 1990 (Lubitz et al., 2002); and major changes, such as use of glycopotein IIb/IIIa together with drug-eluting stents are resulting in more such procedures being performed each year (Mayers et al., 2002).

The magnitude of these mechanisms leads Gelijns and Rosenberg (1991) to conclude that "…*when technological change not only reduces costs but also improves quality, expectations of reductions in aggregate expenditures are likely to be frustrated*…"

d. Broadening definition of "disease"

Vast improvements in the ability to diagnose and treat illnesses are expanding the definition of what an illness is, and the opportunities to deal with problems not conventionally considered as "illnesses". The areas of human conditions treated under "healthcare" are getting wider and wider.

Infertility is now regarded by the medical and social community as a "disease" and, as such, treated and covered by an increasing number of health insurance systems and schemes; this

was not the case before infertility treatments and in vitro fertilisation became technically feasible. The introduction of implantable artificial joints, such as hands, arms and legs, that provide esthetical comfort and some functionality, immediately transformed the related condition into a treatable (to some extent) condition, deserving coverage.

Another striking example of this process, derived from the pharmaceutical field, is that of the treatment of male impotence. With impotence, health status, as conventionally defined, is not at stake; but the advent in 1998 of an effective treatment, Viagra, has in few years expanded the comprehensiveness of what constitutes "healthcare", as confirmed by the product's reimbursement under several schemes and systems.

e. The life-extending effect of new technologies

Life-extending medical technologies deploy their impact on health expenditure also through a computational effect, for which each individual bears (or causes) "more years of yearly expenditure". Through this way, the overall effect of prolonged life might be an increase in life-time health expenditure even in the presence of decreasing average costs and expenditure per year of life (Weisbrod, 1991).

3.5 Medical devices and medical technology: too expensive to be sustainable in the future?

As seen in the previous paragraphs, innovation in medical technology and devices is normally associated with increasing healthcare expenditure. More generally EU public expenditure on health is projected to increase its incidence on GDP by more than 2.5 percentage points in the next five decades.

These key facts suggest a question: despite their proved benefits, are technical innovations in medical devices and in medicine financially sustainable? What kind of policy measures should be enacted to sustain these improvements without constraining the number of beneficiaries and the acquisition and access to significant technologies?

The analysis of the composition and of the long-term sustainability of healthcare expenditure and the broader social expenditure can provide important elements to approach these issues. The following table describes the long-term projections of the main voices of public social expenditure produced by the Ageing Working Group of the Economic Policy Committee of Ecofin (AGW; European Union Economic Policy Committee, 2001 and 2003). Together with healthcare pensions, education and unemployment benefits are also projected. These, as outlined in Box 3, have been projected mainly on the basis of the evolution of the demographic structure.

Table 3. Public social expenditure, 2000 and projections at 2050 - % of GDP

	Base year 2000					Projections at 2050								
	pensions	health care	educat.	unempl. benefits	total	pensions	Δ	health care	Δ	educat.	Δ	unempl. benefits	Δ	total	Δ
Austria	14.5	5.8	6.0	0.7	27.0	17.0	*2.5*	8.6	*2.8*	5.4	*-0.6*	0.6	*-0.1*	31.6	*4.6*
Belgium	10.0	6.1	5.7	2.1	23.9	13.3	*3.3*	8.2	*2.1*	5.3	*-0.4*	1.0	*-1.1*	27.8	*3.9*
Denmark	10.5	8.0	8.6	1.4	28.5	13.3	*2.8*	10.7	*2.7*	7.7	*-0.9*	1.4	*0.0*	33.1	*4.6*
Finland	11.3	6.2	6.1	1.7	25.3	15.9	*4.6*	9.0	*2.8*	6.4	*0.3*	1.4	*-0.3*	32.7	*7.4*
France (1)	12.1	6.9	6.4	1.2	26.6	15.8	*3.7*	8.6	*1.7*	6.4	*0.0*	0.7	*-0.5*	31.5	*4.9*
Germany	11.8	n.a.	5.4	1.1	18.3	16.9	*5.1*	n.a.	n.a	5.6	*0.2*	0.7	*-0.4*	23.2	*4.9*
Greece	12.6	n.a.	4.0	0.4	17.0	24.8	*12.2*	n.a.	n.a	4.5	*0.5*	0.2	*-0.2*	29.5	*12.5*
Ireland	4.6	6.6	4.7	0.8	16.7	9.0	*4.4*	9.1	*2.5*	4.3	*-0.4*	1.0	*0.2*	23.4	*6.7*
Italy	13.8	5.5	4.6	0.3	24.2	14.1	*0.3*	7.4	*1.9*	4.3	*-0.3*	0.2	*-0.1*	26.0	*1.8*
Luxemb.	7.4	n.a.	n.a.	0.2	7.6	9.3	*1.9*	n.a.	n.a	n.a.	n.a.	0.2	*0.0*	9.5	*1.9*
Netherlands	7.9	7.2	5.0	1.3	21.4	13.6	*5.7*	10.4	*3.2*	5.0	*0.0*	1.4	*0.1*	30.4	*9.0*
Portugal	9.8	n.a.	5.6	0.7	16.1	13.2	*3.4*	n.a.	n.a	5.3	*-0.3*	0.6	*-0.1*	19.1	*3.0*
Spain	9.4	n.a.	5.0	1.4	15.8	17.3	*7.9*	n.a.	n.a	3.7	*-1.3*	0.4	*-1.0*	21.4	*5.6*
Sweden	9.0	8.8	7.8	1.4	27.0	10.7	*1.7*	11.8	*3.0*	6.7	*-1.1*	1.1	*-0.3*	30.3	*3.3*
UK	5.5	6.3	5.3	0.3	17.4	4.4	*-1.1*	8.1	*1.8*	5.9	*0.6*	0.4	*0.1*	18.8	*1.4*
UE-15	10.0	6.7	5.7	1.0	20.9	13.9	*3.9*	9.2	*2.5*	5.5	*-0.3*	0.8	*-0.2*	25.9	*5.0*

(1) Pension spending is projected at 2040 rather than 2050.

Source: European Union Economic Policy Committee (2001, 2003).

The figures reveal that:

- in 2000, almost half of the EU public social expenditure consisted of pensions; pensions are also projected to record the highest expenditure growth at 2050 (+3.9 percentage points vs. 2.5 of healthcare);
- though not shown in the table (but see Union Economic Policy Committee, 2001 and 2003), while the profile of the incidence of pensions is curbed over the period of projection and tends to stabilise in the long run, this does not happen for healthcare, where the profile is slowly but continuously rising. Moreover, the projected path is to be considered as the lower limit of the actual expected path: besides the effect of innovation, on which we elaborated in Box 3, also "demand effects" might lead to stronger pressures than those projected, since the base may contain some unexpressed or "truncated" demand.

The considerations above suggest that, independently from technological innovation in medicine and medical devices, EU Members will be asked to adopt significant reforms of their social security systems, in order to ensure both their financial and social sustainability (the latter being the adequacy of benefits and services, in terms of their diffusion and modernization[16]).

[16] The European Council of Barcelona (see Council of The European Union, 2003) designing the main lines of action in reforming European pension systems suggested pursuing three goals: long term financial sustainability, adequacy of benefits and modernisation, in a wide sense, of the system. These goals can be extended to the entire set of social expenditures.

The general framework of policy mix normally identified by theory and practice (see for example Diamond, 2000; Miles and Sefton, 2002; Pammolli, Oglialoro and Salerno, 2004) to reach these goals consists in the so called "triple diversification" of the expenditure:

I. a rebalancing within the components of public social expenditure, in order to better encounter new needs and demand; in particular, in many EU Member States public expenditure is, and is projected to be, too concentrated on pensions;

II. a rebalancing between public and private sources of financing through the adoption of co-payment schemes. This with the aim not only of reinforcing the equilibrium of public finances, but also of creating the right incentives for cost-effective consumption of public goods and services;

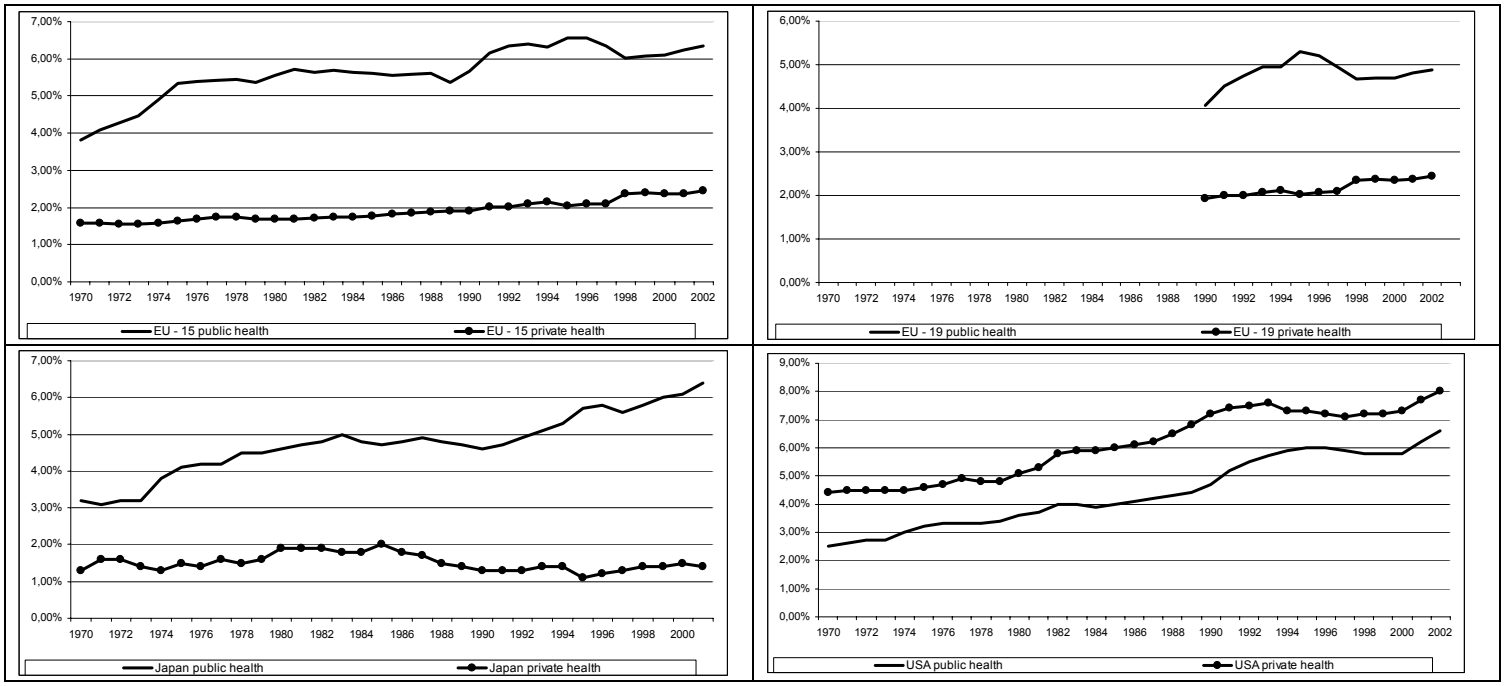
III. a rebalancing within the composition of private social expenditure, in order to strengthen the organised institutional pillars of pension and healthcare funds (to be achieved also under the impulse of favourable taxation).

These three aspects of diversification complement each other. Their achievement will preserve the fundamental goals of the social system and optimise the mix of its financing.

As for the last point, a vast economic literature (Miles and Cerny, 2006; OECD, 1998, 2001, 2005; Modigliani and Muralidhar, 2004; Boeri and Perotti, 2002; OECD, 1998, 2001, 2005; Feldstein and Liebman, 2001; Barr, 2001) has pointed out the benefits associated to a diversified – private and public – and well-balanced financing structure. These benefits emerge under a dynamic point of view, where the two financing channels, public and private, play a different role: public financing, based on taxation and social contributions, evolves mainly in line with labour productivity; private financing, managed by fund managers, is instead connected to capital productivity. A balanced combination of public and private financing allows more moderate taxation. In this it contributes to higher employment and to labour productivity as well as to higher investments and capital productivity through the more efficient allocation of resources on the financial markets.

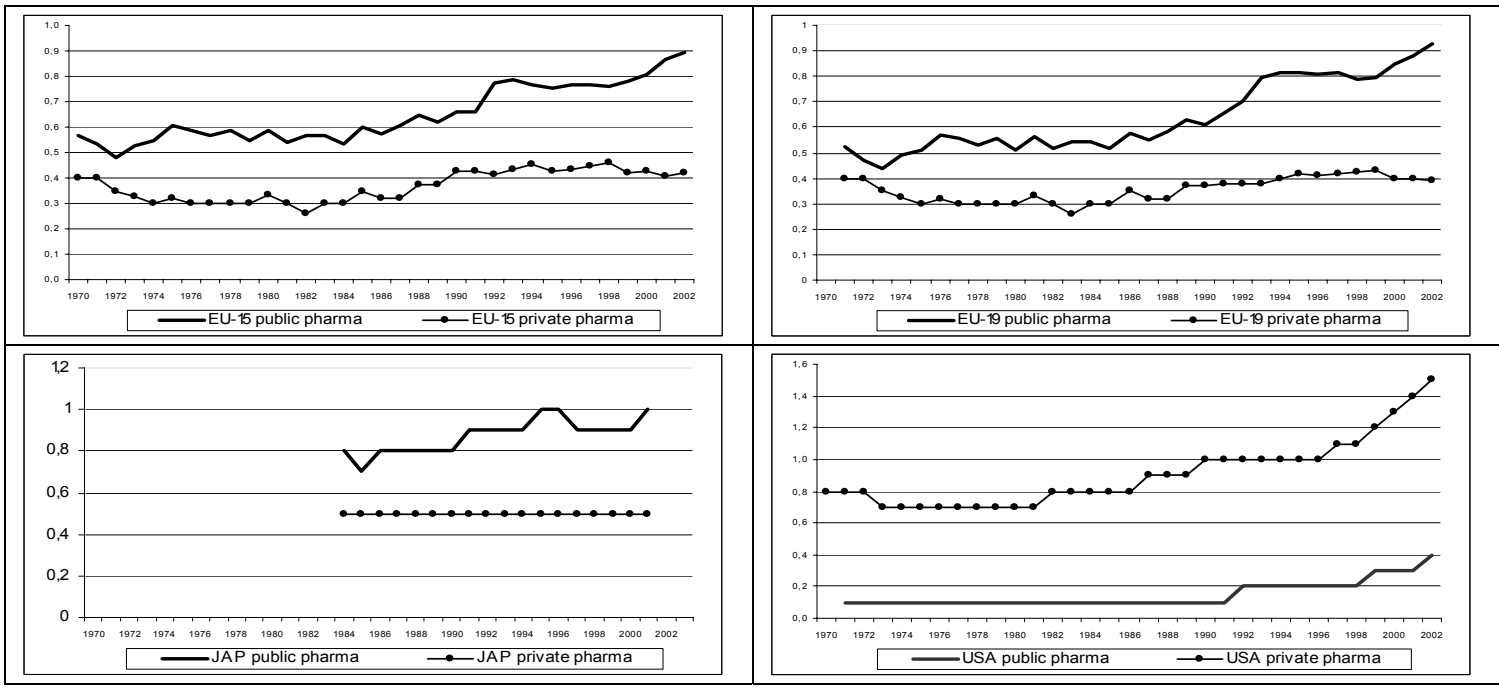
As can be seen from Figures 5 and 6, the complementarity between public and private funding for health has been so far scarcely exploited in Europe and Japan compared to the US. For EU-15, EU-19 and Japan, the historical evolution of health and pharmaceutical expenditure shows a growing spread and asynchronism between public and private components. On the contrary, a clear co-evolution appears for the US, where public and private expenditure appear as integrated.

Figure 5. Long-term trends of public and private healthcare expenditure (% of GDP)



Source: OECD Health Data (2004).

Figure 6. Comparison between public and private pharmaceutical expenditure – 1970-2002, % of GDP



Source: OECD Health Data (2004).

The breakdown of private healthcare expenditure in Table 4 shows the different relevance of the private institutional pillar in the EU and US. Private expenditure in Europe consists largely of out-of-pocket payments by patients: almost 70 percent in 2002, compared to about

25 percent for the US. In the US, the percentage covered by the private institutional pillars is over 65 percent, whereas in Europe it is approximately equal to 17 percent.

Table 4. Composition of private healthcare expenditure – 1980, 2002, % of GDP

	1980			2002		
		institutionalised			institutionalised	
	out of pocket by households	insurance contracts and health funds	mutual organiz.	out of pocket by households	insurance contracts and health funds	mutual organiz.
Canada	58.9	3.2	26.3	50.3	3.8	38.4
France	64.0	17.4	28.5	40.9	19.9	35.0
Germany	48.5	27.5		48.2	39.9	
Italy	64.5	3.0		83.3	3.7	
Japan	90.2		2.5	89.9		1.5
Spain	83.2	15.9		82.5	14.5	
UK	80.8	12.3		64.4	19.2	
US	41.4	48.5		25.4	65.7	
EU-15	68.3	15.6		68.8	17.1	

Source: authors' calculations from OECD Health Data (2004).

Note: mutual organisations work as a pay-as-you go system in which, as in the public health systems, members' contributions pay for those members who need healthcare; on the contrary, insurance contracts and health funds work on a insurance financial basis.

From a policy point of view, the underdevelopment of the institutional pillars assigns the burden of financing healthcare directly to households, without the "screen" of any specific and organic tax relief scheme; when adverse events occur, households need to pay out of pocket at least part of the treatment; this prevents the establishment of a direct and long-term connection between the resources devoted to healthcare goals, efficient allocations on capital markets and investments that are a key driving force for economic growth.

EU Member States appear to have margins to strengthen the diversification of the financing sources for the long-term sustainability of healthcare expenditures. With the appropriate use of market regulation and fiscal incentives and support to the disadvantaged categories of patients, this structural change can take place preserving the fundamental social choices.

Treatments based on innovative medical devices can be interested by the diversification of financing for at least two aspects:

- a diversified financial structure could partially loosen budget constraints as well as the focus on cost-containment. This would allow more room for high price-performance products both in the public and private markets;
- the industry of medical devices and of high-tech medicine can be one of the investment targets for health funds and benefit from a significant financial source for R&D and innovation.

To sum up, the debate on the impact and sustainability of medical device expenditures needs to be enriched in order to include elements related to social expenditure composition and overall sustainability. The best way to approach the problem is to consider it as part of the economic reforms that will regard welfare systems next years, attempting to combine together

the so-called gold quartet: welfare diffusion, long-term financial stability, competitiveness and growth.

4. ECONOMIC EVALUATION OF MEDICAL DEVICES: SOME CASE STUDIES

Summary of the chapter

The objective of this chapter is to present some examples of the impact of medical device innovations on the whole health system. In particular, we are interested in the evaluation of economic implications deriving from the adoption of innovations in medicine.

Far from being an exhaustive review of all the possible innovative technologies, we focus here on four specific situations: the interventional market for cardiology, diabetes mellitus and blood glucose control, osteoarthritis and the prevention of breast cancer.

Besides their relevance in terms of population affected by those pathologies, each of these cases witnessed the (relatively) recent introduction of highly innovative devices, which somehow produced a massive change in the way that the pathology is treated, both on a clinical and on an economic level.

A common feature of all the case studies presented here is that, although these innovations typically proved a certain degree of clinical effectiveness improvement, economic evaluations led to more controversy. As a matter of fact, the short-term analysis almost always suggests that moving from standard (previous) treatments towards innovative ones can produce a significant increase in the overall costs associated to that pathology.

However, despite these cases being characterised by different levels of heterogeneity, in all the situations that we considered here, when evaluated in the long-term, all the new devices are likely to be associated with some cost-effectiveness results. In particular, a proper economic analysis also allows to take into account relevant subpopulations (i.e. the high risk patients, however defined), among which the use of the innovative device becomes extremely cost-effective. A more rational allocation of resources is warranted in this way, as suggested by some of the evidence we presented here.

4.1 Introduction

The last twenty years have witnessed a massive interest in health technology assessment. The ageing of world population and the introduction of high-cost as well as high-performance innovations in medicine have increased the necessity of health services to monitor the financial impact of new technologies adopted, versus their therapeutic impact. This process has been initiated in the US system, during the late 1970s, but soon spread to European countries, and is now a widely accepted concept in all healthcare systems.

At present, economic concepts are quite standard in this framework, thanks to the contributions of many scholars (e.g., Drummond et al, 1997, Donabedian, 1988 and Phelps, 2003). For instance, classic analysis involves the evaluation of the *costs* associated with a given programme with respect to either the *effectiveness* (as measured by some suitable clinical proxies), or the *benefits* (in terms of utility, whatsoever specified) for society, derived by the utilisation of such innovations. Great care is needed in the definition of these concepts. As an example, costs involved could be only direct (i.e. that of acquisition and usage of the technology, as well as those derived by side effects), or could be extended to include also the indirect costs, associated with loss of work, home care and patients' poor quality of life.

Recently, statistical research has focused massively on health economics topics, producing considerable advances in estimation techniques (see for example the works of O'Hagan and Stevens, 2001 and 2003, and that of Briggs, 1994). As a result, health economists are now equipped with tools that enable long-term evaluations that can jointly consider several parameters (such as the interaction of costs and clinical effectiveness). In addition, uncertainty derived by economic estimations can be taken into account properly (i.e. by means of probabilistic sensitivity analysis, Spiegelhalter et al., 2004). On the other hand, the need of systematic data collection, directly focusing on both cost and clinical effectiveness measures, is increasing in importance and massively advocated.

In this section, we will illustrate some case studies of technological innovations in medicine, associated with medical devices. The objective of this section is to identify some archetypical examples of:

a) The effectiveness of an innovation on health outcomes;

b) The huge heterogeneity of the innovation process;

c) The market structure.

We will rely on methodology and findings of health technology assessment applied to the technology under examination.

The case studies that we present in the following are representative of some areas of medicine, which for different reasons, play a major role in health systems. Our intention is by no means that of producing a comprehensive review of all the areas covered by innovation in medicine. The main criteria that guided our selection of cases are: *a)* the impact on the population, in terms of patients affected by a given pathology; *b)* the economic burden associated with the treatment of that pathology; and *c)* the innovative characteristics of the technology and associated product.

The technologies illustrated here are:

1. Interventional cardiology market: the case of drug eluting stents;
2. Diabetes treatment and blood glucose control;
3. Osteoarthritis and total hip replacement;
4. Imaging devices for mammography.

Of course, other areas could fit into the criteria that we defined in order to select the cases. However, we decided to concentrate on the ones described above because of the high relevance that is perceived.

Each case study is presented as follows:

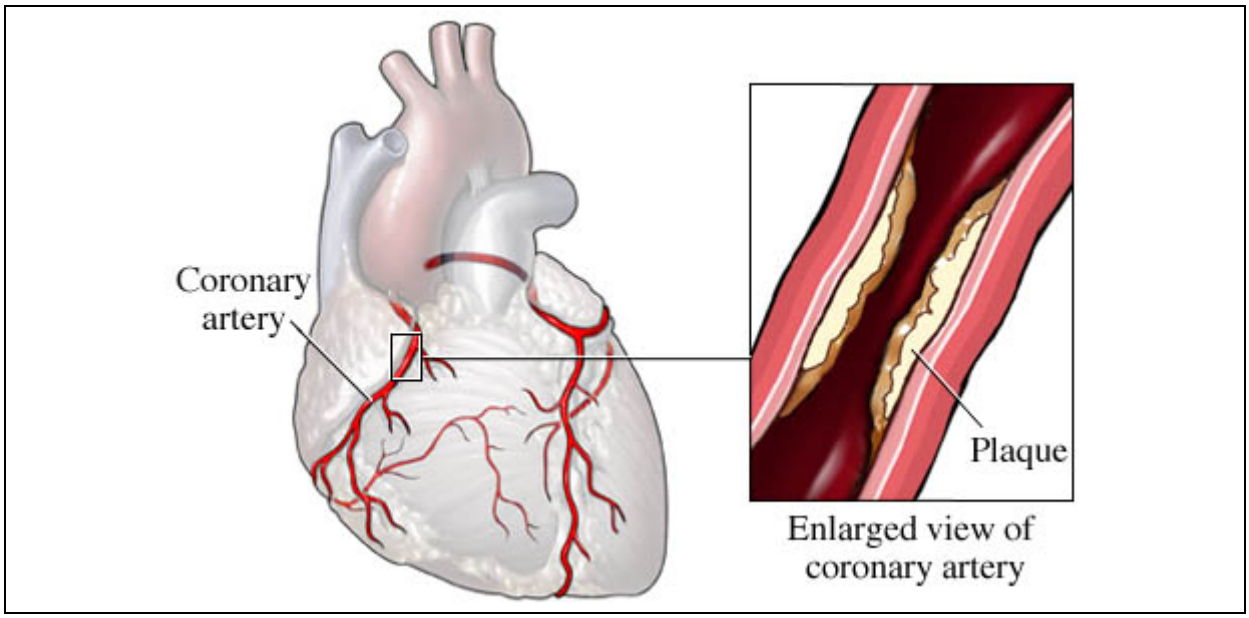
a. Brief description of the pathology associated with the innovation, and its prevalent therapeutic protocols;
b. Relevance of the pathology: population affected and costs associated;
c. Background to innovation: history, previous standards and technologies;
d. Innovation: description, impact on health and on costs.

4.2 Interventional Cardiology Market: the case of Drug Eluting Stents

a. Brief description of the pathology associated with the innovation and prevalent therapeutic protocols

Coronary artery disease (CAD) occurs when the arteries that supply blood to the heart muscle (coronary arteries) become hardened and narrowed, due to the build-up of plaques on the inner walls or lining of the arteries (atherosclerosis). Blood flow to the heart is reduced as plaques narrow the coronary arteries, leading to a decrease of the oxygen supply to the heart muscle (Figure 1).

Figure 1. How Coronary Artery Disease develops



Source: Mount Auburn Hospital Website (2005).

CAD is the most common type of heart disease, and the leading cause of death in the US in both men and women.

The set of available treatments comprises of three major programmes:

- *Medications*, such as cholesterol lowering drugs, beta blockers, angiotensin converting enzyme, and other pharmaceutical treatments;
- *Open heart surgery*, including bypass and laser revascularisation;
- *Minimally invasive surgery*, such as angioplasty.

Angioplasty, as a minimally invasive procedure, is performed under local anaesthesia. A balloon catheter (i.e. a small tubing system fitted with a deflated balloon at its extremity) is introduced in the arterial vasculature, through the groin and is guided to the coronary arteries via the aorta. The doctor visualises the balloon catheter navigating into the artery with an X-Ray imaging system.

The balloon catheter is then positioned at the site of the narrowing and the balloon is briefly inflated pushing and reorganising the plaque, i.e. the fatty deposit obstructing the arteries.

The balloon is then deflated and retrieved, leaving an enlarged artery and restoring normal blood flow. The entire procedure may last up to an hour and the patient can be discharged from the hospital on the same day or the day after.

b. Relevance of the pathology: population affected and costs associated

An estimated 17 million people die of Cardiovascular Disease (CVD), particularly heart attacks and strokes, every year (WHO, 2004a). A substantial number of these deaths can be attributed to smoking, which increases the risk of dying from coronary heart disease and cerebrovascular disease by 2–3 fold. Physical inactivity and poor diet are other risk factor, which increase individual risks to cardiovascular diseases.

Nearly half (49 percent) of all deaths are from CVD (55 percent of deaths in women and 43 percent deaths in men). The main forms of CVD are CAD (also known as 'ischemic diseases') and stroke. About half of all deaths from CVD derive from CAD and nearly a third from stroke (see Tables A.4.1–A.4.3). CAD by itself is the most common cause of death in Europe: accounting for nearly two million deaths each year. Over one in five women (22 percent) and men (21 percent) die from the disease.

There are wide variations in mortality rates across Europe: eastern countries reach eight CVD related death per 1,000, while southern countries reach only three to four CVD-related deaths per 1,000. The picture is not that different for other major countries such as the US, or Japan. Tables A.4.1 to A.4.3 depict some information about prevalence and incidence of cardiovascular diseases, both in general and with specific focus on CAD.

According to the American Heart Association and the National Heart, Lung, and Blood Institute the direct and indirect costs of cardiovascular diseases and stroke in the US for 2004 are estimated at $368.4 billion. As for the EU, a recent Eurohealth report estimated the direct and indirect economic cost of CVD to be between €70 and €135 billion per year.[17] More specifically, Shearer et al (2004) find that the total direct healthcare cost of CAD in the UK in 2001 was estimated to be approximately £1,8 billion (about €2.64 billion). The largest cost components were drug treatment (70 percent) and hospital treatment (25 percent).

c. Background to innovation: history, previous standards and technologies;

The history of the treatment of CAD dates back at least to the nineteenth century. However, the latest 30 years have witnessed at least three blasting innovations, which determined a sensible change in the practice of the treatment of this pathology.

The first one can be identified with the work of Dr. Andreas Greuntzig, a German physician working in Switzerland, who in 1977 inserted a balloon catheter into a patient's coronary artery, successfully opened a blockage and restored blood flow to the heart. This was the first *percutaneous transluminal coronary angioplasty* (PTCA). A decade later, PTCA – a minimally invasive technique – took off in Europe, and rapidly established itself as one of the most common surgical procedures, all over the world.

Although extremely successful, balloon angioplasty had limitations, mainly due to restenosis or re–narrowing of the treated lesions. Restenosis requires re–intervention, which usually occurs within nine months following the initial procedure. With PTCA, which is the standard

[17] This figure includes both direct and indirect costs. Direct costs include the cost of physicians and other professionals, hospital and nursing home services, the cost of medications, home healthcare and other medical durables. Indirect costs include lost productivity that results from illness and death.

intervention, this side effect can occur in as many as 30 percent of the treated patients. Restenosis can be caused either by elastic recoil (75 percent), or neo-intimal proliferation (25 percent). Elastic recoil is a mechanical reaction of the artery that springs back after it has been forced open during the PTCA procedure. Neo-intimal proliferation, which is similar to a scar tissue, is a biological response to the mechanical injury resulting from the procedure, or in other words, a healing process.

In the first half of the 1990s, a second major innovation was introduced in the market. *Stents* were developed to try to solve the restenosis problem. A stent is a tiny metallic mesh with tubular shapes that is inserted into the artery using PTCA techniques, and acts like a mechanical scaffold that limits re-narrowing of the artery. Following the introduction of stents, restenosis rates dropped in the 15 percent – 20 percent range.

Therefore, the stent market noticeably took off in Europe in the second half of the 1990's, and landmark clinical trials established the superiority of stents over balloons**.**

At the beginning of the new century, stents were able to cope brilliantly with all the mechanical issues. However, restenosis also involves a biological process during which scar tissues form inside the stent and reduce blood flow. Hence, to address this biological process, *drug–eluting stents* were developed.

d. Innovation: description, impact on health and on costs

Drug eluting stents (DES) represent one of the most innovative developments in interventional cardiology. This device associates an anti-proliferate drug to prevent scar tissue formation, a drug delivery system to release the active drug at a specific rate and a stent to carry both the drug and the drug delivery system and to act as a mechanical scaffold.

As a result, the risk of incurring in restenosis is highly reduced: the landmark trial RAVEL (Serruys et al, 2002) was the first one to compare conventional stents with DES and demonstrated an impressive 0 percent restenosis rate in the DES arm. Later, other studies were performed, which showed low (though not null) prevalence of restenosis in patients treated with DES; as compared to standard stent procedure, DES can reduce the risk of restenosis up to 75 percent. (Weaver et al, 2000; Rinfret et al, 2001; Leon et al, 2002).

The expansion of the market for DES can be explained by the fact that, from the clinical point of view, the introduction of DES had the effect of allowing physicians to treat patients that present more complex conditions. These include diabetic patients, and individuals with smaller vessels and more extensive plaques in the artery, who were treated by means of invasive surgery, before the introduction of DES. This circumstance translated in a huge increase in the quality of life.

However, although clinical benefits of DES are increasingly evident, important concerns about their costs have been raised in the medical community.

The main issue is related to the fact that the clinical target of DES procedure – the reduction of restenosis – is mainly a secondary outcome. In fact, to date, no study has demonstrated a convincing link between restenosis and mortality. Consequently, despite the clear clinical benefits, concerns remain on whether the additional costs associated with the elimination of restenosis are worth paying.

The unit cost of a DES was estimated as $2,700 per stent procedure, whereas standard balloon PCI only has an average cost of $700 (Greenberg et al, 2004). Lemos et al (2004) attribute this incremental costs to factors associated with the innovative process such as:

a) *Higher R&D costs*, as testified by the relatively high concentration of the market. In Europe, the main four companies account for more than 85 percent of total revenues;

b) *Acquisition of exclusive and valuable licenses from pharmaceutical companies*; this factor has a huge impact in the strategic alliances of the companies, and determines a high level of competition among the main companies;

c) *New manufacturing facilities needed*; as an example, Boston Scientific (market leader in Europe) has made an investment and exclusive option to purchase arrangement with REVA Medical, Inc. of San Diego, which is currently working on new generation DES;

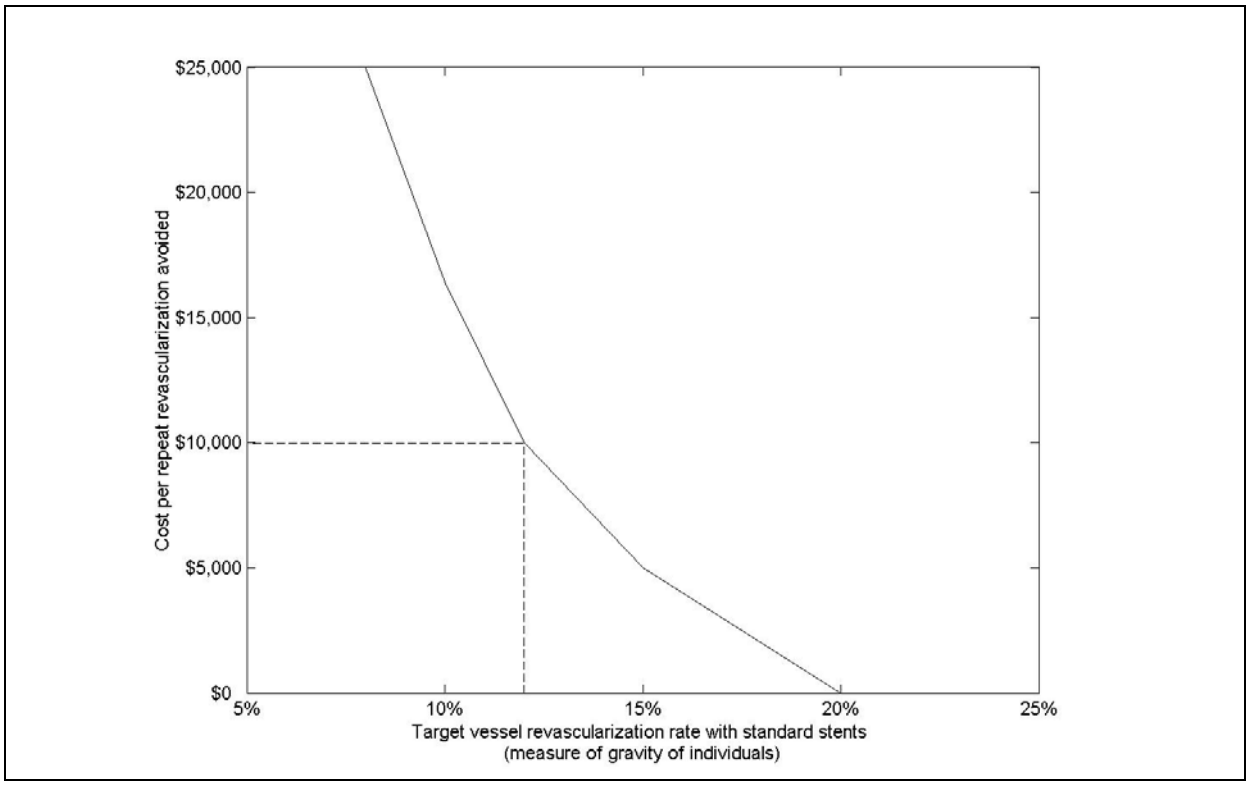
d) *Low production levels*; although increasing at relevant rates, as of 2003, DES only represent a limited share of total PCI procedures.

As appears straightforward, the higher short-period costs associated with DES has major implications on the economic point of view. Greenberg et al (2004) estimate that uniform conversion of all current standard stent procedures to DES will result in a cost increase of about $2,800 per patient treated, whereas Lemos et al (2003) calculated that the unrestricted usage of DES in the patients that currently receive standard stents would cost the US system about $1.5 billion each year.

However, several cost effectiveness analyses performed on sub-groups of patients with different initial clinical conditions demonstrated that DES could result in cost savings, when applied to medium-high risk patients. For instance, van Hout et al (2002) and Greenberg et al (2004) showed that treatment with DES could be cost effective for patients with estimated re-intervention likelihood greater than 12 percent, and even result in cost savings for patients with estimated re-intervention likelihood greater than 20 percent (see Figure 2). Moreover, it has to be considered that the therapeutic alternative for these patients is surgery, which is an expensive procedure, besides being invasive.

For this reason, other studies have focused on the comparison between DES and Coronary Artery Bypass Grafts (CABG) surgery. On the one hand, the effectiveness level of CABG is still superior, as compared to both standard and drug eluting stents (Hirshfeld and Wilensky, 2004). However, on the other hand, DES have narrowed the efficacy gap, and in addition they also have improved significantly the quality of life of patients. Consequently, DES could turn to be cost saving, in case the expansion on the market is to the detriment of the highly expensive CABGs (Lemos et al, 2003).

Figure 2. Cost effectiveness of DES, as compared to standard stent procedure (a cost per event averted less than $10,000 is considered as indicative of cost effective procedure)



Adapted from Greenberg et al. (2004)

Yet, some analysists forecast that much of the DES market growth will occur at the expense of the BMS market. This circumstance inevitably leads to the necessity of re-designing the distribution of budgets and priority for the whole health system.

A problem related to this issue is that suggested by O'Neill and Leon (2003), who reports some estimations made at the William Beaumont Hospital, MI (US). The penetration of DES in place of CABG would lead to *a)* fewer repeat procedures; *b)* fewer repeat bypasses; and *c)* higher total costs associated with DES procedure. This is perceived as a huge barrier to entry, and appears to generate noticeable problems with reimbursement activity.

Furthermore, the decreased demand of standard stents will intensify price erosion among manufacturers competing for shares in a declining market.

Conclusions

Drug eluting stents proved to be a highly effective device in reducing the risk of restenosis. This feature is highly valuable, especially for patients who present complex conditions, such as diabetes, or particularly extensive lesions.

The positive results in clinical trials will help DES establish in the market and in fact the penetration rate is estimated on 60.5 percent of all stented procedures by the year 2008. Market profitability is high, due to premium prices, which are associated with DES, since their clear innovativeness. However, this also leads to high prices, which, in conjunction with the poor reimbursement regulation, generate a barrier to the diffusion of DES.

From the perspective of healthcare providers, the available evidence suggests so far that DES are in fact a cost effective procedure for high risk patients, although unrestricted access to this new technology can generate increases in healthcare costs, in the short-term.

4.3 Diabetes Mellitus and glucose control

a. Brief description of the pathology associated with the innovation and prevalent therapeutic protocols

Diabetes mellitus is a medical disorder characterised by varying or persistent hyperglycaemia (elevated blood sugar levels), especially after eating. While there are different types of diabetes mellitus, most are asymptomatic for a (variable) time after onset, but all share similar symptomatology and complications at advanced stages. This disease involves multiple casual factors and clinical aspects, all of which should be well understood for better management.

Hyperglycaemia itself can lead to two severe complications, such as dehydration and ketoacidosis, which is a deficiency in insulin. Before the introduction of clinical insulin, back in 1922, the mortality rate for ketoacidosis was 100 percent; nowadays, it is only about 2 percent (Bell and Alele, 1997).

Longer-term complications include cardiovascular disease (doubled risk – equal rates to those with heart attacks from advanced atherosclerotic disease), renal failure (worldwide, diabetes mellitus is the most common cause of chronic renal failure requiring renal dialysis), retinal damage with eventual blindness, nerve damage and eventual gangrene with probable loss of toes, feet, and even legs.

Historically, physicians have focused on the following factors that are characteristic of diabetes mellitus: *a)* decreased production of insulin, *b)* decreased sensitivity of body tissues to insulin (the most common), or *c)* a combination of both. The distinction between these circumstances remains important, and characterises the two main forms of diabetes:

- *Type 1 diabetes*: (formerly known as 'insulin-dependent') in which the pancreas fails to produce the insulin, which is essential for survival. This form develops most frequently in children and adolescents, but is being increasingly noted later in life.
- *Type 2 diabetes*: (formerly named 'non-insulin-dependent'), which results from the body's inability to respond properly to the action of insulin produced by the pancreas. Type 2 diabetes is much more common and accounts for around 90 percent of all diabetes cases worldwide. It occurs most frequently in adults, but is being noted increasingly in adolescents as well.

Even in terms of therapeutic standards, the two forms of diabetes, though sharing some common features, are characterised by different procedures.

Type 1 patients were the first to be identified, and the treatment is insulin supply, e.g. by means of injections. Additional drugs can be used by those patients to cope with concomitant conditions, even if these further treatments are not directly related to glucose control.

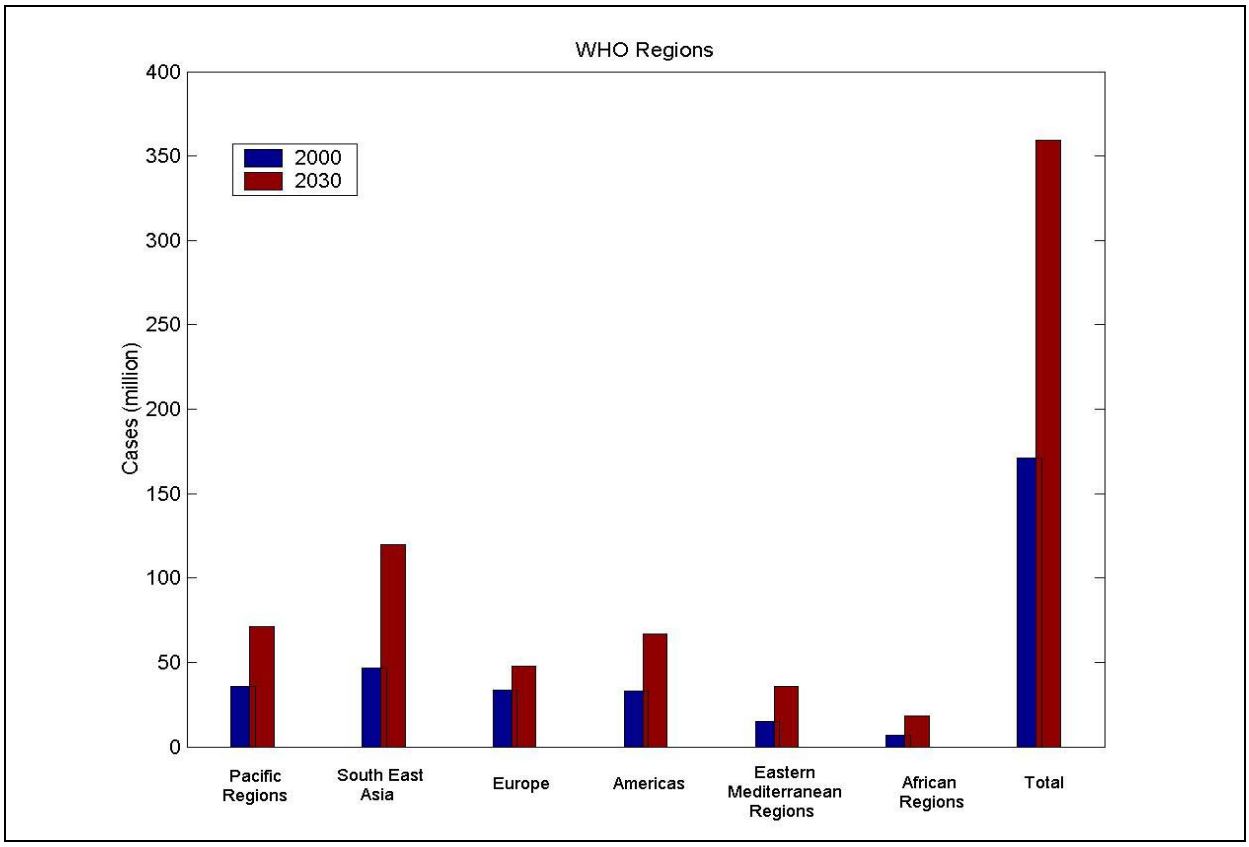
Besides the use of insulin and testing, which are common features with Type 1 patients, individuals suffering from Type 2 diabetes are also treated with hypoglycaemic drugs. Testing procedures involve specific devices, along with particular diet regimes and physical activity.

b. Relevance of the pathology: population affected and costs associated

According to the World Health Organisation (2004b), in the year 2004, more than 150 million people worldwide suffer from diabetes. The incidence of the pathology is increasing rapidly, and it is estimated that by the year 2030 this number will double (see Figure 3).

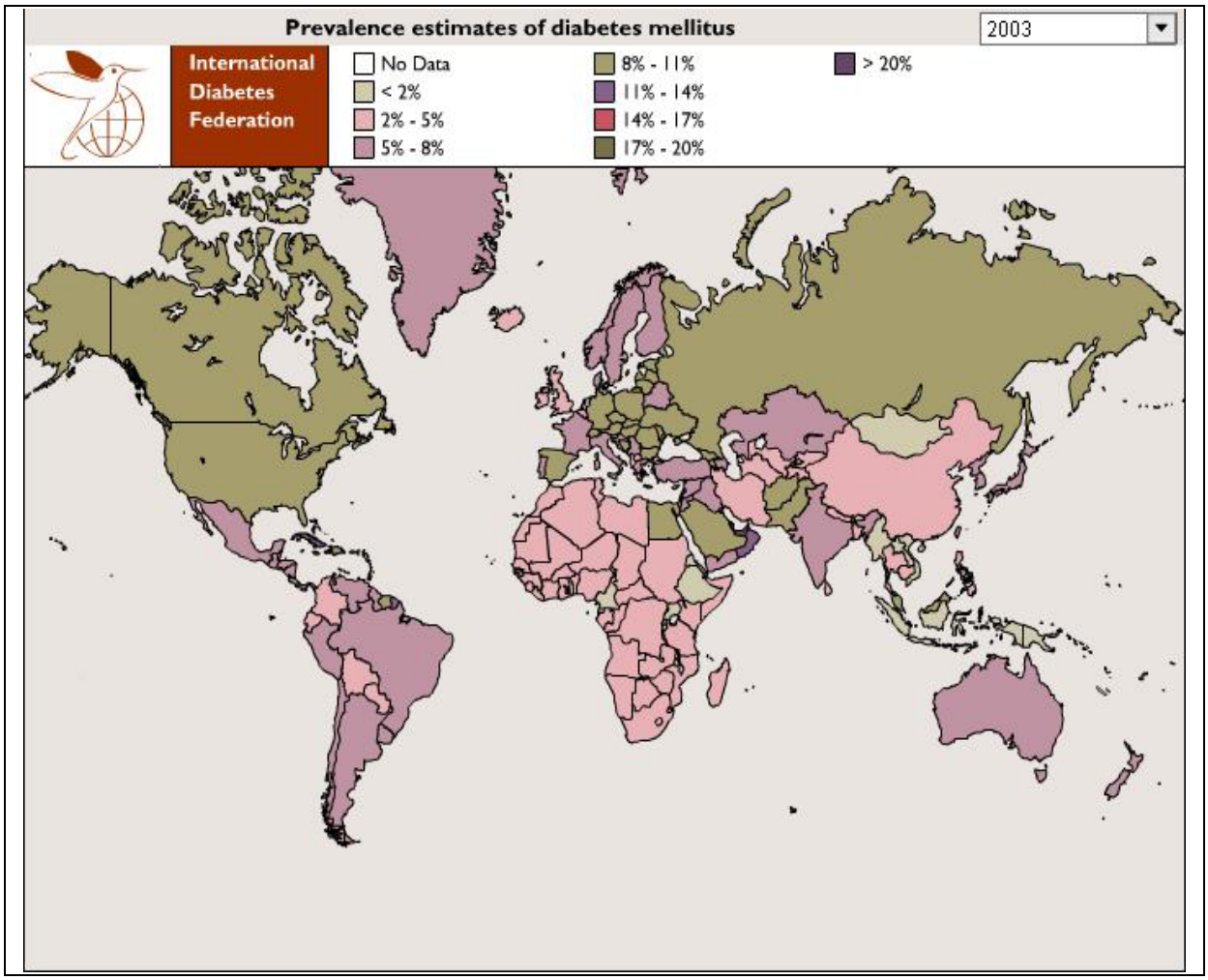
Diabetes mellitus occurs throughout the world, but is more common (especially Type 2) in the more developed countries (see Figure 4). In 2002, there were about 18.2 million diabetics in the United States alone (WHO, 2004b), and for at least 20 years, diabetes rates in North America have been increasing substantially.

Figure 3. Diabetes mellitus prevalence. Data observed in 2000 and forecasts for 2030.



Source: WHO (2004b).

Figure 4. Prevalence estimates of diabetes mellitus, 2003



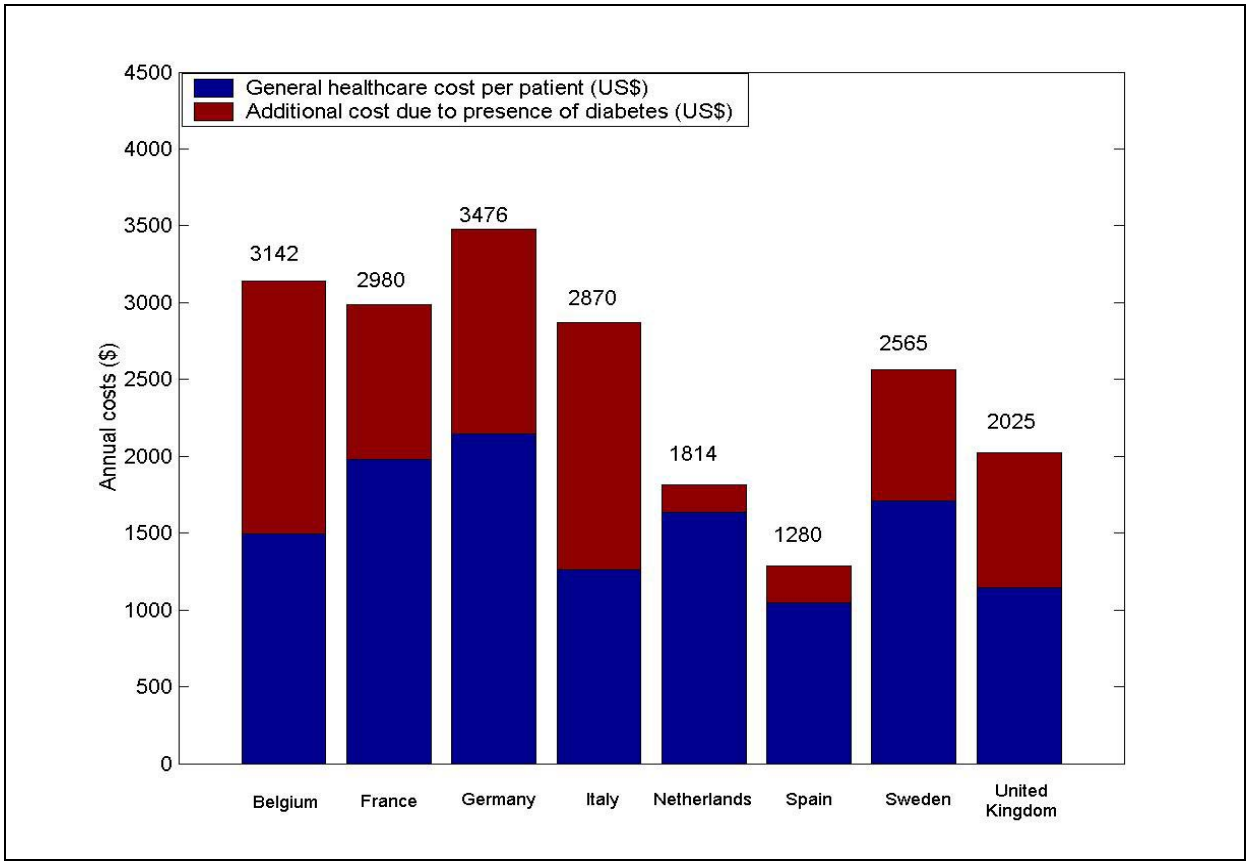
Source: International Diabetes Federation (2004).

Mortality rates in patients with diabetes mellitus are higher than those in the general population, and life expectancy in both type 1 and type 2 diabetes are reduced by 25 percent, as reported by the International Diabetes Federation (IDF, 2004). Currently, the number of deaths related to the disease has been estimated at just over 800,000 a year, worldwide, but the real figure is thought to be more in the region of 4 million a year. In contrast to the general population, the mortality rate among female diabetic patients is almost identical to that of males, and the increased mortality is mainly attributable to cardiovascular disease and renal failure.

As for the economic burden of the disease, the American Diabetes Association (2003) estimate that diabetes costs $132 billion in the United States alone every year. IDF (2004) reports the annual cost for diabetic patients in some selected European Countries (see Figure 5). Combining their estimation with the figures for the diabetic population (WHO, 2004b), we calculated a total estimated burden for Europe of $84 billion.

While increasing in incidence, Type 1 diabetes already represents a substantial burden to health systems: Evans et al (2000) report that this disease accounts for over £ 35 million in the UK drug budget.

Figure 5. Annual costs of diabetes in Europe, 2000



Source: International Diabetes Federation (2000).

Garattini et al (2004) estimated the total direct cost associated with patients with type 1 and type 2 diabetes, from a multi-centres study. Patients on type 1 diabetes were associated with a cost of €136, whereas the cost for patients on type 2 diabetes was estimated at €123, suggesting that, although being less frequent, type 1 diabetes can lead to higher direct consumption of health resources.

c. Background to innovation: history, previous standards and technologies

Although diabetes has been known since antiquity, and treatments were known since the Middle Ages, the elucidation of the pathogenesis of diabetes occurred mainly in the 20th century.

Despite this, diabetes remains a chronic disease with no standard pharmacological cure (except experimentally in Type 1 diabetics) as of 2004, even if some procedures exist, which usually to manage it effectively.

In the last fifteen years, two clinical studies have produced major insights on diabetes management.

The Diabetes Control and Complications Trial (DCCT, 1993) is a clinical study conducted from 1983 to 1993 by the National Institute of Diabetes and Digestive and Kidney Diseases. The study showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of eye, kidney, and nerve diseases caused by diabetes.

The study compared the effects of two treatment regimens – standard therapy and intensive control – on the complications of diabetes. Volunteers were randomly assigned to each treatment group, showing the following results:

- A reduction in new eye disease risk of about 76 percent;
- Worsening of existing eye disease risk reduction of 54 percent;
- Early kidney disease risk reduced by 54 percent;
- More serious kidney problems reduce by 39 percent, and
- Nerve damage risk reduction of 60 percent.

The second important study was the UK Prospective Diabetes Study (UKPDS, 1998), the largest trial ever done on Type 2 diabetics, a very complicated trial lasting over 20 years, with multiple sub–studies. Its major contribution was to highlight the importance of tight control of both blood pressure and glucose levels, in order to reduce long-term complications of Type 2 diabetes, showing:

- Heart disease risk reduced by 56 percent;
- Stroke risk reduced by 44 percent;
- Kidney disease risk reduced by up to 33 percent, and
- Eye disease risk reduction of 33 percent.

Insulin pump therapy

As Type 1 patients lack insulin, their therapy consists in insulin replacement. Initially, enough insulin to prevent ketoacidosis and minimise symptoms was thought to be an adequate treatment.

Unlike other medicines, insulin cannot be taken orally, since in the gastrointestinal tract it is treated precisely as any other protein, i.e. it is reduced to its amino acid components, whereupon all 'insulin activity' is lost. There are research efforts underway to develop methods of protecting insulin from the digestive tract so that it can be taken orally, but none has yet reached clinical use. Given these circumstances, different routes of administrations had to be used.

Until the 1970s, insulin was usually taken as subcutaneous injections by single-use syringes with needles, and patients needed to inject insulin several times a day (at least two), every day of their life. This was obviously perceived as a demanding treatment, contributing to a poor quality of life.

Efforts were done, in order to light the load of patients, in terms of the number of injections, and to increase the effectiveness: a typical example is the introduction of pen injectors in the early 1980s. These are rather like ink cartridge pens in design, and contain a cartridge of insulin. Pens are the predominant insulin delivery system in most parts of the world, except the United States where syringes still dominate.

In 1993, the DCCT trial showed that giving insulin was not enough, but mimicking the normal insulin secretion pattern of non–diabetic individuals was the real target. The trial compared conventional insulin injections to Multiple Daily Injection (MDI), and showed that the former had superior clinical benefits. After that, MDI became a very popular medication,

even if in the US market more than 50 percent of Type 1 patients still use one to two injections per day. This therapy has been classified as *sub-optimal* (DeWitt and Hirsh, 2003).

A further innovation in the field is represented by Continuous Subcutaneous Insulin Infusion (CSII), which recent studies (cfr. Lenhard and Reeves, 2001 and Pickup et al., 2002) proved to provide superior glycaemic control, as compared to MDI.

Self Management of Blood Glucose

Based on the available literature, a recent guideline (Goldstein et al., 2004) reported that all treatment programs should encourage Self management of Blood Glucose (SMBG), as this strategy can help most patients with type 1 diabetes achieve the goal of maintaining blood glucose levels as close to normal as is safely possible. For this reason, SMGB is considered an integrated part of disease management in diabetes treatment, and specific devices have been introduced in the market to this aim.

Glucose self-monitoring began in 1941 with the introduction of urine testing. In the 1950s, Ames Company, a division of Miles Laboratories in Elkhart, Indiana, introduced strips to test for glucose in the urine, with the result being determined by comparing the colour change generated on the strip with colour patches.

Urine testing was the standard of care for many years, until 1965, when blood glucose testing began using the Ames Dextrostix system, a visually read paper strip. Accurate assessment of the resulting colour change by purely visual analysis was found to be a problem and, therefore, the company introduced a meter to read the strip, for use in doctors' practices. This meter – the Ames Reflectance Meter – was first used by a patient at home in 1970. The result was given as a numerical outcome, via a swinging needle.

The first widely available meter, the Eyetone, manufactured in Japan by Kyoto Daiichi Kagaku (KDK), was sold by Ames from 1972. As self-monitoring became more popular, more companies began to produce progressively more and more advanced meters. Boehringer Mannheim developed the Chemstrip strips, and later the first Accu-Chek meter to read those strips. LifeScan produced its first meter in 1980.

Until the late 1980s, *reflectance photometry* was the only technology used for blood glucose monitoring. This technique worked by quantifying the intensity of a coloured product generated by the conversion of glucose via an enzyme catalyst, the amount of coloured product produced being directly related to the amount of glucose in the sample.

MediSense laboratories were the first company to introduce a system based on *Electrochemistry*, a technique that quantifies the number of electrons generated by the reaction of glucose with a mediator via an enzyme catalyst. The number of electrons captured by the mediator is directly proportional to the amount of glucose present in the sample. A voltage is applied to the mediator, which transfers the electrons to the electrode, where they are counted. All major companies in the sector have adopted this technology, and it is slowly replacing reflectance technology as the preferred method of measurement.

d. Innovation: description, impact on health and on costs

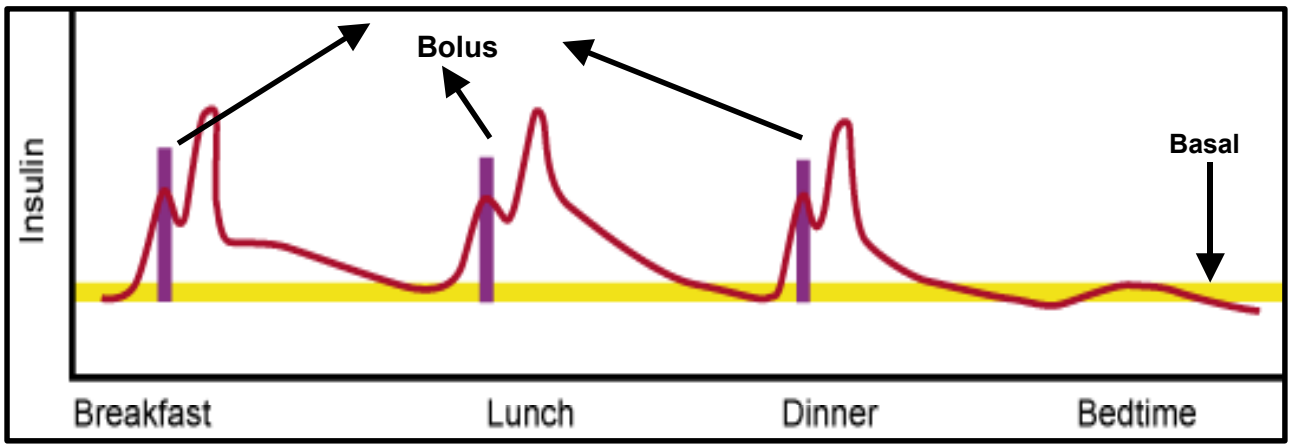
Insulin pump therapy

CSII is provided by an insulin pump, made up of a pump reservoir filled with insulin, a small battery-operated pump and a computer chip that allows the user to control exactly how much insulin the pump delivers. It is all contained in a plastic case about the size of a beeper.

The pump reservoir delivers insulin to the body by a thin plastic tube called 'infusion set'. Infusion sets come in 24 inch and 42 inch (respectively, 60 and 106 cm) lengths and have a needle or soft cannula at the end, through which the insulin flows. Most people prefer the soft cannula, especially since insertion is virtually painless with the automatic inserter. The cannula is inserted just under the skin, usually into the abdomen. The process of putting the infusion set in place is called 'insertion', and is very much like giving a standard insulin injection. The infusion set is changed approximately every two to three days. As a result, as compared to injections, patients need only a single operation in three days, instead of six in the same period.

The pump is used continuously and delivers insulin 24 hours a day according to a programmed plan, which is uniquely defined for each pump user. A small amount of insulin is given continually (the 'basal rate'). This insulin keeps blood glucose in the desired range between meals and over night. When food is eaten, the user programs the pump to deliver a 'bolus dose' of insulin matched to the amount of food that will be consumed, as depicted in Figure 6.

Figure 6. How insulin pump infusion matches physiologic insulin secretion



From the clinical point of view, CSII proved to significantly decrease the level of glycaeted haemoglobins, resulting in higher effectiveness (Pickup et al., 2002). Weissberg et al (2003) performed a meta analysis on 52 studies, and show that CSII decreased significantly more glycaeted haemoglobins level than MDI, with a difference of 0,95. Linkeshova et al. (2002) performed a long-term prospective study, and found out that CSII has a significantly positive impact on quality of life parameters, as depicted in Table A.4.5. Moreover, CSII proves important in the control of hypoglycaemia. Recent works (Linkeshova et al., 2002; Weissberg–Benchell et al., 2003) suggest in fact a substantial decreased frequency of hypoglycaemic episodes in patients associated with CSII therapy.

From the economic point of view, not many studies allow a direct comparison between MDI and CSII. In fact, none of the most important trials – the DCCT and the UKPDS – are directly focused on economic evaluation. Roze et al (2005) estimated a total annual cost of £ 2,641 for CSII therapy, as compared to £ 1,482 for MDI. However, given the estimated increase in the effectiveness measure analysed (quality adjusted life expectancy, QALE) of about 0.76 (±0.19) years, the incremental cost effectiveness ratio (ICER) for CSII vs MDI was calculated at £ 25,648/ QALEs. This value is slightly above the current threshold defined by NICE to assess the cost effectiveness of an intervention (ICER < £ 20.000). Therefore, besides being a clinically effective intervention, CSII therapy can be considered to represent good value for money.

Self-Management of Blood Glucose

The principle of all blood glucose monitoring devices is virtually the same: a small blood sample is collected to a test strip by the patient, using a lancing device (a sterile pointed needle). This test strip contains various chemicals that, when the blood is applied, create a small electrical charge between two contacts. This charge will vary depending on the glucose levels within the blood and its effect on the chemicals contained within the strip. In older glucose meters, the drop of blood is placed on top of a strip. A chemical reaction occurs and the strip changes colour. The meter then measures the colour of the strip optically.

However, not every meter suits all patients, and moreover, the last technological advances allowed meters to become progressively smaller, faster and easier to use, with smaller blood volumes being one of the greatest advances. Even over the last 5 years, test times have reduced from 45 seconds to only 5 seconds, and sample size from 10µl to less than 1µl.

All of these advances have increased the acceptance of SMBG by patients and, as a result, its usage has grown enormously. This circumstance is highly relevant, both from the clinical and the economic point of view.

At present, there are many (at least 20) different types of blood monitoring devices available on the market today. Competition between manufacturers is intense, with new offerings coming to the market on average every 6 months or so, and product life-cycles being relatively short (2-5 years depending on the product's market acceptance).

Despite the difficulty of doing so, investment in trying to find a device that is capable of being utilised by most types of patient is significant, with each manufacturer looking for the general-purpose device. Patients tend to replace their meter every 3-4 years, and therefore there are more than 2 million individuals looking to acquire a new device each year, so that the potential return on investment is significant for those devices that are accepted. However, the market entry criteria are becoming more challenging.

In several EU countries blood glucose meters are not covered by reimbursement and their cost is transferred on the consumable component of the testing system, the test strip, which is reimbursed for most people with diabetes in the EU.

With the complexity of devices increasing, as well as the cost of R&D, this barrier to market-entry can represent a disincentive for some companies to participate in this area. However, there have been several recent entrants on the market, and in-licensing is also considered a good opportunity.

As an alternative means of market access, companies are increasingly selling meters via retail pharmacies. Although more attractive in financial terms as compared to the provision of free

of charge meters, prices are low (around $10-20) and insufficient to cover the cost of manufacture.

Both distribution channels can prove costly in terms of the necessary sales and marketing support needed to ensure awareness and advocacy. These costs are increasing as companies expand sales teams and expand marketing activities to cover direct to consumer promotion, including, in some EU countries, television advertising. An idea of the relevance of this market is given by the fact that the impact of the glucose monitoring market is estimated at around $3 billion.

Convenience has been the major area of focus for product development over the last 5 years or so. There have been no significant improvements in the testing process, rather companies have concentrated on making the procedure faster and easier and less painful, with huge benefits for diabetic patients.

A recent innovation, utilised only by two manufacturers so far, has been the incorporation of the test strips into a cartridge, which is then inserted into the device. Using this sort of mechanism eliminates the need to insert individual strips into the meter prior to testing, and to carry additional test strips around. Even though this advance appears to offer greater patient convenience, the mechanical reliability of these devices has been questioned and to date they have only achieved a relatively small combined market share (approximately 7 percent at the end of 2003).

At the market level, the industry is characterised by a set of major companies, accounting for about 80 percent of the market. The rest can be seen as residual. Moreover, there is huge interaction with innovations in other areas (i.e. Electrochemistry).

From the clinical point of view, the availability of medical treatments for diabetes means that excellent blood glucose control is achievable. This feature can also have a huge impact on the economic point of view, as long-term complications can take years to develop, so with excellent diabetes care it should be possible to avoid the great majority of these problems.

The DCCT Trial (1993) involved two groups of patients with Type 1 diabetes, one of which was maintained on an intensive insulin regime aimed at keeping blood glucose at near normal levels with the other being treated conventionally. The standard measure of glucose control is the Glycated Haemoglobins (HbA1c) test, which shows how well the blood glucose levels were controlled during the previous 3-month period. Although the DCCT study did not analyse the direct effect of Self-Monitoring of Blood Glucose (SMBG) on patient outcomes, it seems that appropriate daily self monitoring of blood glucose levels did contribute to effective intensive insulin therapy and hence the HbA1c improvements reported. The study results demonstrated that intensive therapy reduced the risk of eye disease, diabetic kidney disease and diabetic neuropathy.

Following these findings, UKPDS (1998) studied more than 5.000 people with Type 2 diabetes and aimed at maintaining a group of patients on a similarly intensive therapy designed to maintain near normal blood glucose levels. The study also showed that intensive glucose control could reduce the risk of both diabetic retinopathy and diabetic neuropathy.

Table A.4.6 summarises the results of these two studies, in terms of their effect on the rate of complications (notice that the former study was concerned with type 1 patients, whereas the latter was focused on type 2 patients, which explains the difference in the rates reported).

Other studies have assessed the direct effect of SMBG on disease progression, such as that of Nyomba et al (2003), which looked at the effect of SMBG on glycaemic control. The main

finding was that when patients had unrestricted access to testing supplies, they were better able to control their glucose levels (as determined by measuring HbA1c levels) than were those patients who did not. Moreover, insulin dose did not change significantly in patients in the former group, whereas in the latter group the dose increased 1.5 fold over the duration of the study.

Soumerai et al (2004) assessed the effect of SMBG on medication compliance. Initiating SMBG was associated with increased regularity in the use of medications and a reduction in high blood glucose levels that are associated with diabetes complications.

The economic impact of SMBG has been investigated by UKPDS (2000). Their findings are that intensive glucose control increased trial treatment costs by £695 (95 percent confidence interval: £555 to £836) per patient. However, the costs of complications were reduced by £957 (£233 to £1,681), as compared with conventional management.

Furthermore, UKPDS (2001) confirmed these results, reporting that intensive blood glucose control with metformin produced a net saving of £258 per patient, over the trial period (mean duration 19.7 years), again due to lower complication costs and increased life expectancy by 0.4 years.

Conclusions

Diabetes mellitus is associated with various forms of heterogeneity, both in terms of patients' characteristics, and of related treatments. Consequently, clinical and economic evaluations should be focused precisely on specific aspects.

However, the evidence that we found in medical and economic literature tends to suggest the following conclusions:

- Despite the high heterogeneity, a set of standard treatments can be identified for both type 1 and type 2 patients. These health programs are likely to involve continuous innovations, in order to meet the demand for better quality of life coming from diabetes patients.
- This feature is quite important, since, on the one hand, the prevalence of diabetes is constantly increasing through the entire world, and, on the other hand, younger patients are being affected from this disease. Those individuals are likely to be in their full working and physical activity, generating a demand for minimally invasive procedures.
- When measured in the long-term and considering patients' quality of life as a relevant effectiveness measure, the introduction of different innovations in medicine and in-vitro diagnostic can prove to be associated with lower costs.

However, some concerns are increasingly arising with respect to reimbursement policies, which are substantially different in the US to other markets. This feature can possibly perturb the dynamics of diabetes markets, and need careful examinations by means of central authorities.

4.4 Osteoarthritis and Total Hip Replacement

a. Brief description of the pathology associated with the innovation and prevalent therapeutic protocols

Osteoarthritis (OA) is a major cause of pain and disability, particularly in older people, as worldwide it accounts for half of all chronic conditions in person aged 65 and older, and one in four people over the age of 60 have significant pain and disability from osteoarthritis.

OA is a degenerative arthritis process, which determines the breakdown of the joints cartilage, the part of the joint that cushions the ends of bones. Cartilage breakdown causes bones to rub against each other, causing pain and loss of movement. OA can range from very mild to very severe, and it affects weight–bearing joints such as knees, hips, ankles, foot joints and the back.

Many factors can cause OA: although age is a risk factor, research has shown that OA is not an inevitable part of aging: for instance, obesity may lead to osteoarthritis of the knees. In addition, people with joint injuries due to sports, work–related activity or accidents may be at increased risk of developing OA. Even genetics have a role in the development of this condition, i.e. some people may be born with defective cartilage or with slight defects in the way that joints fit together.

As a person ages, these defects may cause early cartilage breakdown in the joint, and in the process of cartilage breakdown, there may be some inflammation, with enzymes released and more cartilage damage.

The treatment of OA focuses on decreasing pain and improving joint movement, and may include:

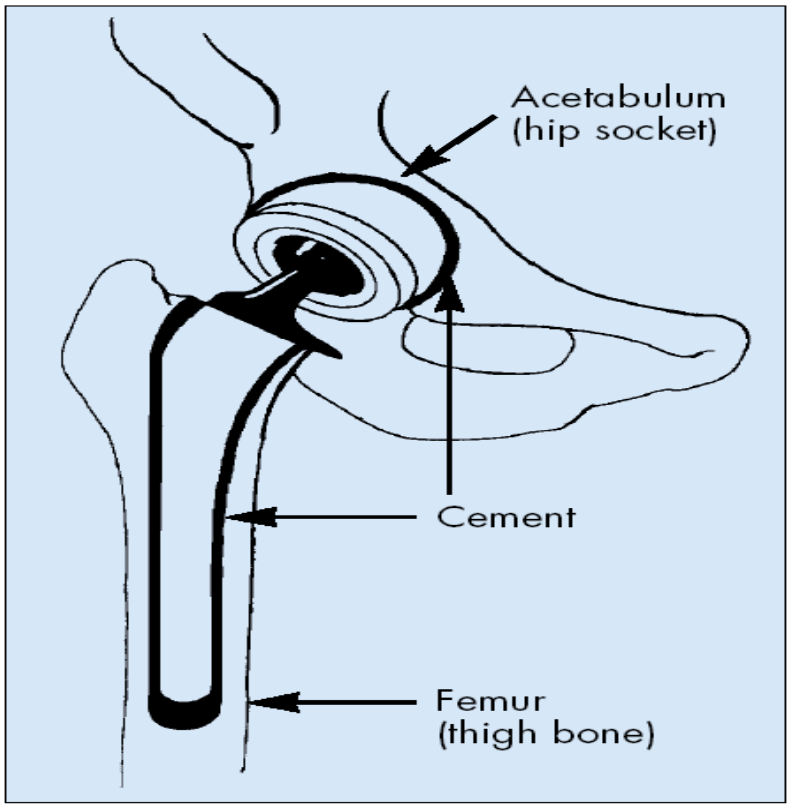
- Exercises to keep joints flexible and improve muscle strength;
- Many different medications to control pain, including corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids injected into joints that are inflamed and not responsive to NSAIDs. For mild pain without inflammation, acetaminophen may be used;
- Heat/cold therapy for temporary pain relief;
- Joint protection to prevent strain or stress on painful joints;
- Weight control to prevent extra stress on weight-bearing joints;
- Surgery, to relieve chronic pain in damaged joints.

Through pain, loss of sleep and decreased functional ability, osteoarthritis has a profound effect on the sufferer. The impairment in terms of global health and functional capacity of a patient with OA is equivalent to that of individuals with chronic renal failure on haemodialysis, or patients with intractable angina secondary to ischaemic heart disease (Canadian Erythropoetin Study Group, CESG, 1990).

Once the patient's condition has progressed beyond conservative management, joint replacement surgery is the treatment of choice. During the 1990s, increases in rates of Total Hip Replacements (THR) have been reported in Scandinavia (Lucht, 2000; Havelin et al, 2000), Australia (Wells et al, 2002) and the United States (Dixon et al, 2004).

A hip replacement is a surgical procedure performed for the relief of pain and the restoration of function in patients with end-stage arthritis of the hip joint. This involves fitting patients with a hip prosthesis (see Figure 7).

Figure 7. Cemented total hip replacement

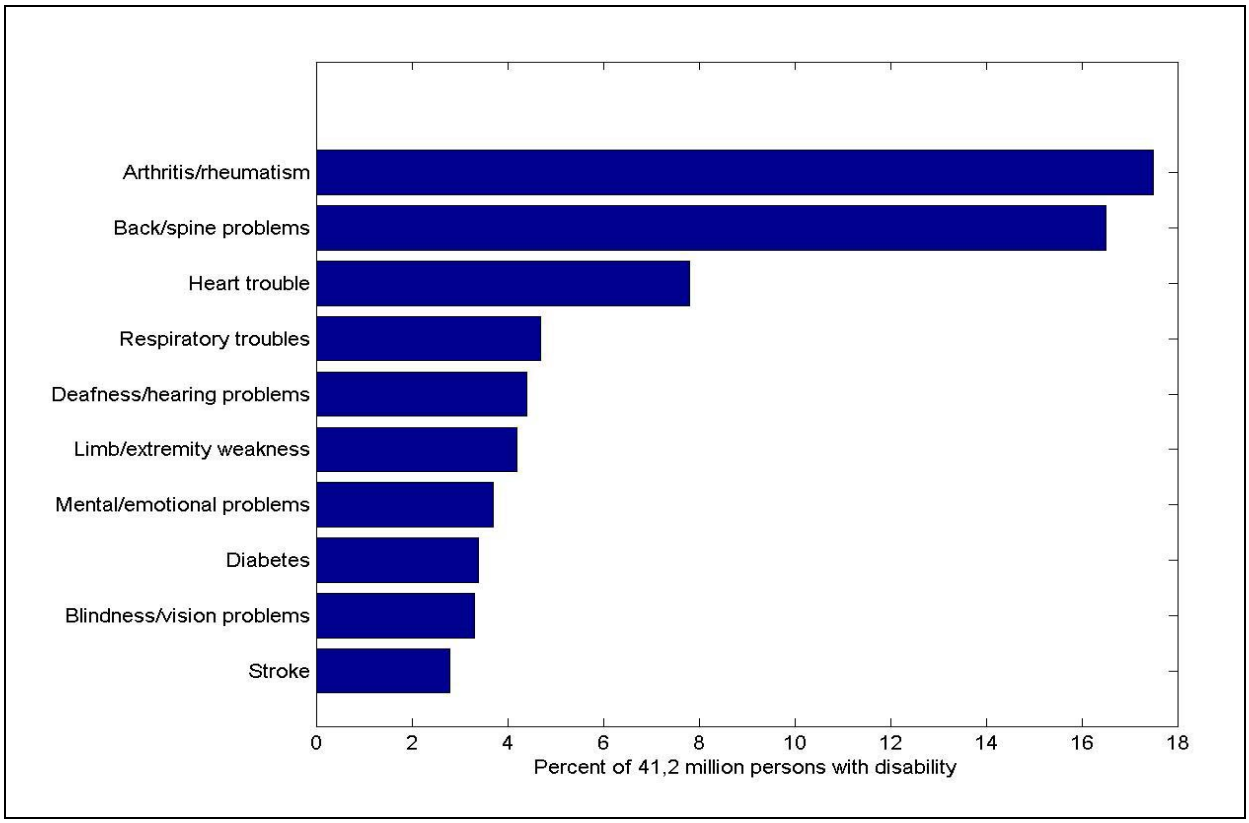


b. Relevance of the pathology: population affected and costs associated

Currently, 103 million people are living with arthritis in Europe, the largest population living with this long-term medical condition in the world (World Health Organisation, WHO, 2000). By 2010, for the first time in Europe, there will be more people over 60 years of age than people less than 20, resulting in a huge escalation of treatment costs, which presents an enormous challenge to health services across all Member States.

Osteoarthritis affects an estimated 20.7 million people in the US, mostly over the age of 45, and is responsible for more than 7 million physician visits per year. Figure 8 shows how arthritis is the leading cause of disability among American adults.

Figure 8. Leading causes of disability among US adults, 1999



Source: MMWR (2001).

Musculoskeletal conditions such as OA cost the US economy nearly $125 billion per year in direct expenses and lost wages and production, as reported by The Arthritis Foundation. In the United States, OA is rated the highest cause of work loss, despite being a condition that causes most problems to populations after retirement age, indicating a wider impact over the population.

An important issue to bear in mind with conditions such as OA is the indirect impact on health status, e.g. the inability to enjoy leisure activities or a reduction in ability to work and activities of daily living. The impact of arthritis is often underestimated because of the difficulties in quantifying many of these consequences.

c. Background to innovation: history, previous standards and technologies

The first devices implanted to replace the arthritic hip were made of a variety of materials that were placed between the degenerated joint surfaces. In 1923, Dr. Marius Smith-Peterson, of Massachusetts General Hospital, used a glass cup to cover and reshape an arthritic femoral head. Although the original glass cup design failed, it led to the development of similarly shaped implants of strong and durable plastic and then metal materials. The next stage was the development of subsequent metallic femoral devices with anatomically sized heads and variable femoral stems.

While many surgeons and bioengineers contributed to the concepts, techniques and designs of implants for total hip replacement, one pioneer stands out, Sir John Charnley, who reported

his experience with a steel femoral component and a plastic socket cup in 1961. He also revolutionised the field with the use of the self-curing acrylic cement used to fix the implants into the bone. These advances greatly improved the success rate of total hip replacement, and the Charnley concepts of hip implants are still in use today.

Charnley's innovative procedure was immediately successful, and rapidly disseminated into routine practice. Consequently, there has been a steady increase in the numbers of patients undergoing total hip replacement in Europe (see for instance Figure 9). As a result, death rates after hip replacement dramatically decreased, from the 1970s, to the 1980s and 1990s (Figure 10). In the 1990s, the mortality rate was 0.15 percent, about 1 in 700 operations.

Figure 9. Trend in the number of THRs in NHS hospitals, England 1967/2001

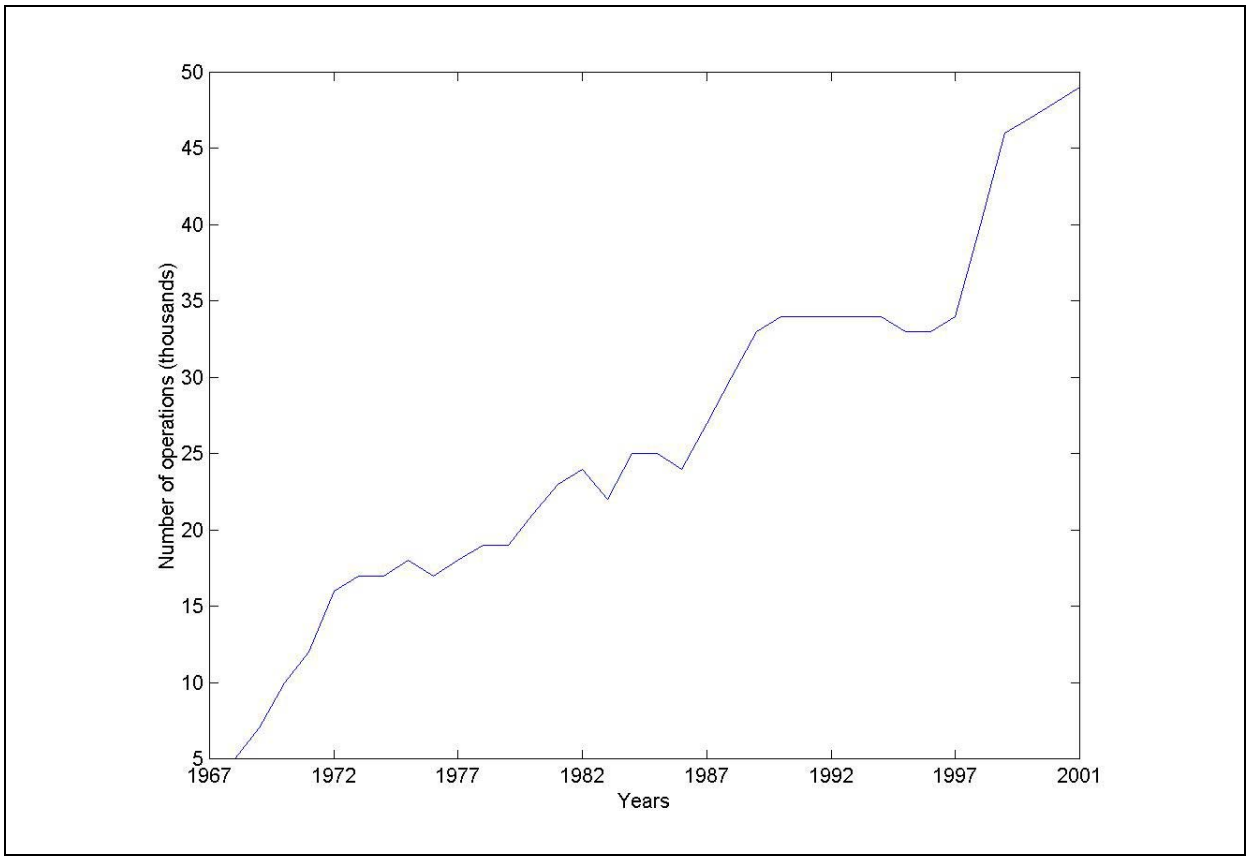
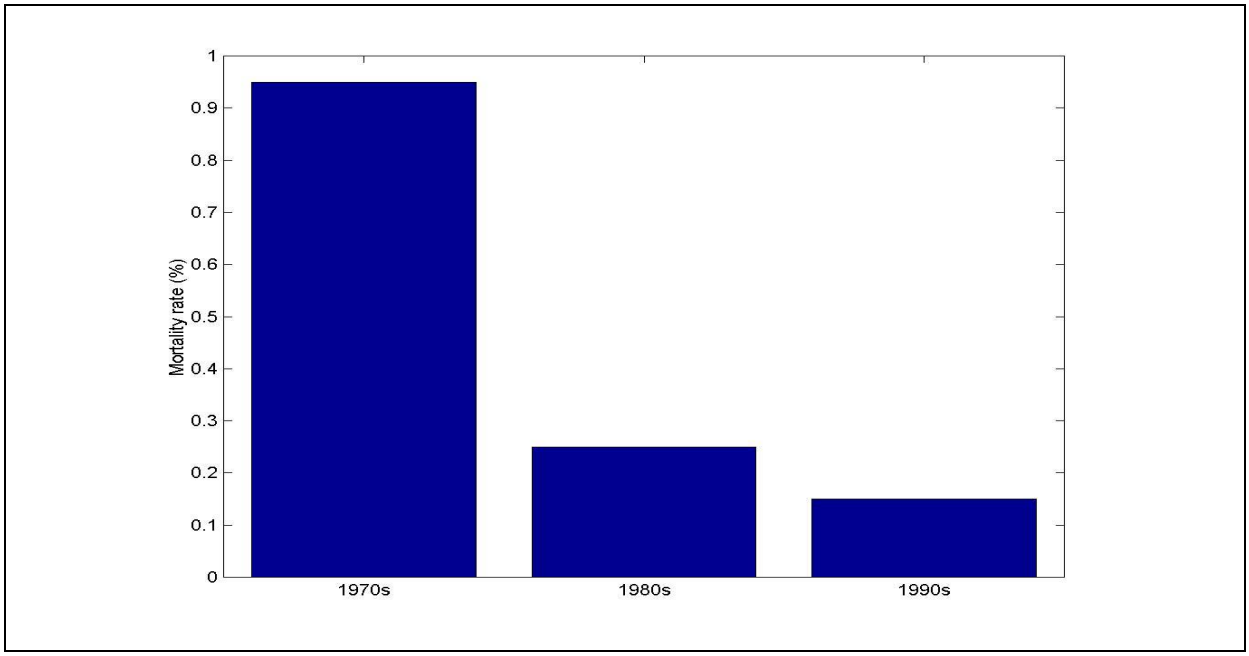


Figure 10. Total hip replacement – 30 days mortality from the 1970s to the 1990s



However, a major problem with cemented hips was aseptic loosening, which was recognised as a long–term issue, related to the generation of polyethylene wear particles, especially in more active males and younger patients. Besides a decrease in prosthesis functionality, this problem can also cause a foreign body reaction with osteolysis (i.e. bone dissolving). Aseptic loosening is a cause of pain and bone loss with the result that the patient needs to undergo revision surgery to fit another prosthesis.

d. Innovation: description, impact on health and on costs

The industry activity and innovation can be summarised by means of the following two areas.

1) *Innovations as incremental activity on traditional surgery*;
2) *Production of lesser and lesser invasive surgery.*

As for the first area, in the 1980s cementless hip prostheses, fixed by bony ingrowth were firstly developed in the US, in order to address the loosening issue, which at the time was thought to be caused by cement breakdown.

In Europe, an innovative approach was the development of hydroxypatite (HA)–coated cementless implants. HA is a mineral, present in healthy bones and that can stimulate the formation of new bone.

As reported by Furnes et al (2005), HA–coated device copes with the problem of avoiding stem loosening, compared to cemented hip replacement. However, the issue of polyethylene cup wear and subsequent cup loosening remains as a major problem.

One solution has been developed, which represents a further step ahead in the innovative process: the development of newer low–wear bearing surfaces, which are based on using tougher polyethylene, or hard–on–hard materials, such as ceramic–on–ceramic or metal–on–metal.

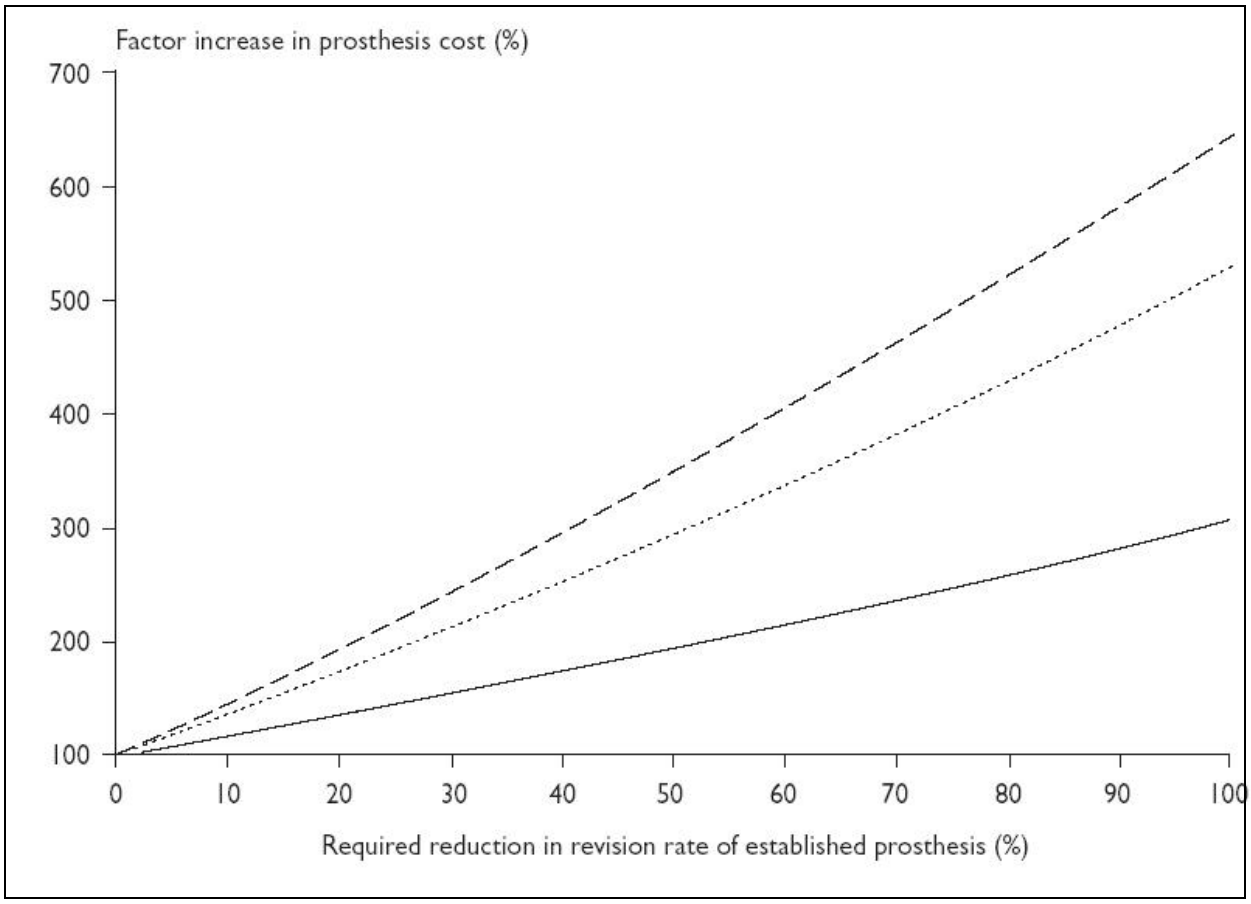
Moreover, the latest development is the use of low–wear–metal–on–metal bearing technology with the introduction of resurfacing hips, which are devices that simply resurface the head of the femur, rather than invasively replacing it with a long–stemmed device.

Of course, this new device is associated with less invasive procedures, as only a part of the bone is resected. This aspect is crucial, and represents the second major area of interest. Furthermore, the level of clinician expertise required to obtain reproducible good outcomes has become higher, with hip replacement surgery being more and more diffused in clinical practice. The introduction of Computer Assisted Surgery (CAS) also led to an increase in the cost-effectiveness of the procedure, after a set up period by improving the precision of the surgery and reducing complications such as dislocation.

Several studies have analysed the economic implications of the development of innovations in THR. For example, Fitzpatrick et al (1998) compared the new cementless prosthesis to the standard Charnley cemented hip. They considered two different scenarios: in the first one, they assumed that innovation is 300 percent more costly than standard, whereas in the second one, the acquisition cost of new technology is to be assumed just 150 percent higher than the older device.

As a result, new procedures did not turn out to be cost-reducing in general. However, if reductions in the revision rate are greater than 50 percent of the baseline, then assuming a threshold cost per quality adjusted life year (QALY) of £6,500, cementless hips produce savings in the medium-long term (see Figure 11).

Figure 11. Two–way threshold analysis to indicate how more effective (in terms of revision rates) a new prosthesis has to be to justify its additional acquisition cost (—: cost neutral threshold; …: £6.500 per QALY threshold; – – –: £10.000 per QALY threshold)



Source: Fitzpatrick et al (1998).

On the other hand, Chang et al (1998) found that cost-effectiveness ratio increases with age, and is higher for men. In a base case scenario for a 60-year-old woman, they predicted that THR is cost saving, because of the high costs of custodial care associated with dependency due to worsening hip osteoarthritis. The procedure would lead to a quality-adjusted life expectancy (QALE) of about 7 additional years.

O'Shea et al (2002) assessed the cost profile of THR in Ireland. The average unit cost was divided into 10 categories, and was estimated at £6,472 per THR performed (see Table A.4.7). Moreover, they used the SF 36 questionnaire (SF 36 Health Survey, 1994) to investigate the utility of THR, in terms of QALYs. The domains showing greatest improvement were *a)* physical functioning; *b)* physical role limitations; *c)* bodily pain; and *d)* social functioning.

One year after intervention, a 10 points increase in the SF 36 scale costs £1,310 for physical functioning, and produces savings of £855 for physical role limitations, of £1,150 for bodily pain, and of £1,245 for social functioning. However, THR did not prove to greatly alter patients' overall health perception, as measured by the SF 36 scale.

Conclusions

It is plausible to assume that on the one hand, THR is an effective procedure, which can be used to treat severe osteoarthritis for all patients. Patients' quality of life of is much increased, and from the clinical point of view, the additional costs related to innovations in the orthopaedic industry are worth paying for.

From the economic point of view, in the case of older patients, the advantages can be found in the reduction of the costs related to disability, such as those of home care. Younger individuals, on the other hand, are mostly associated with indirect benefits, as they are allowed to maintain their physical activity, and keep working. Nevertheless, the cost of intervening on young people has historically been higher, as their higher level of physical activities has led to an increased need for revision (repeat) procedures.

However, the use of the new wear-prevention technologies and more bone-conserving prostheses outlined above should minimise the need for revision surgery for young and old patients alike, reduce its complexity improving patient outcomes and thus lower service costs overall.

4.5 The prevention of breast cancer: mammography

a. Brief description of the pathology associated with the innovation and prevalent therapeutic protocols

Breast cancer (BC) is the most common form of cancer in females worldwide, and in the Western world, it affects approximately 10 percent of all women at some stage of their life. Although significant efforts are made to achieve early detection and effective treatment, about 20 percent of all women with breast cancer will die from the disease, and BC is the second most common cause of cancer deaths in women.

Like all parts of the body, the cells in breasts usually grow and then rest in cycles. The periods of growth and rest in each cell are controlled by genes in the cell's nucleus. When genes are in good working order, they keep cell growth under control. Conversely, when genes develop an abnormality, they sometimes lose their ability to control the cycle of cell growth and rest, leading to cancer.

Cancer has the potential to break through normal breast tissue barriers and spread to other parts of the body. While cancer is always caused by a genetic 'abnormality' (a 'mistake' in the genetic material), only 5-10 percent of cancers are inherited from parents. Instead, 90 percent of breast cancers are due to genetic abnormalities that happen because of the aging process and life in general.

The risk of getting breast cancer increases with age. For a woman who lives to the age of 90 the odds of getting breast cancer her entire lifetime is more than 12.5 percent or 1 in 8 (see Table A.4.8). Men can also develop breast cancer, although their risk is less than 1 in 1000. This risk is modified by many different factors; for instance, in some families, there is a strong inherited familial risk of breast cancer.

Some racial groups have a higher risk of developing breast cancer – notably, women of European and African descent have been noted to have a higher rate of breast cancer than women of Asian origin, as reported by BreastCancer.org (2004). Other established risk factors include having no children, delaying first childbirth, not breastfeeding, early menarche, late

menopause and taking hormone replacement therapy. The probability of breast cancer rises with age but breast cancer tends to be more aggressive when it occurs in younger women.

Two genes, BRCA1 and BRCA2, have been linked to the familial form of breast cancer. Women in families expressing mutations in these genes have a much higher risk of developing breast cancer than women who do not. Together with Li-Fraumeni syndrome (p53 mutations), these genetic aberrations determine around 5 percent of all breast cancer cases, suggesting that the remainder is sporadic.

Depending on the stage at which cancer is detected, standard treatments may vary from surgery to radiation therapy, chemotherapy and immunotherapy. However, the importance of prevention is now well established, and screening is now recommended in many countries as a best practice. Suggested screening methods include Breast Self-Examination (BSE) and mammography. Only mammography has been proven to reduce mortality from breast cancer.

For this reason, mammography is still the modality of choice for screening of early breast cancer. It is the gold standard for other imaging methods such as ultrasound, Magnetic Resonance Imaging (MRI) and Computerised Tomography (CT), which are less useful due to their lower spatial resolution. CT by itself is nearly useless for breast cancer screening as MRI provides better resolution and quality (although it costs much more).

b. Relevance of the pathology: population affected and costs associated

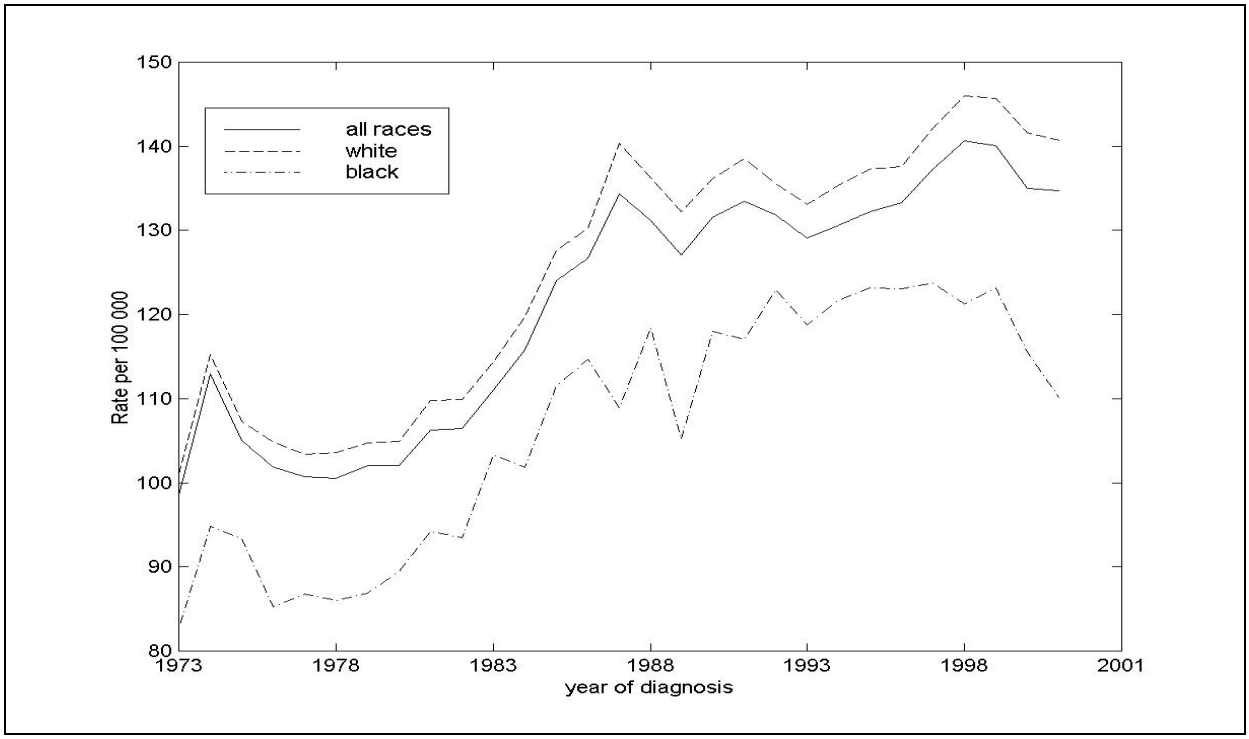
Breast cancer has a huge impact on society, due to its high prevalence. In the US, BC is the most common malignancy in women. Mammography & Beyond (Institute of Medicine – National Research Council, 2001) suggests that each year, more than 180,000 new invasive cases are diagnosed in the United States. Jemal et al (2003) forecasted an even higher incidence of more than 216,000 new cases for the year 2003.

The Surveillance, Epidemiology and End Result Group (SEER, 2004) produced an age-adjusted analysis for incidence and mortality rates in the US; as depicted in Figure 12 and 13, in the year 2001, they estimated an incidence rate of about 135,000 cases and about 26,000 deaths. Moreover, significant differences were suggested with respect to women of race: the incidence rates for black women were lower than those for white women, whereas mortality rates were increasingly higher for black women, starting from the 1980s.

These figures are consistent with those produced by Ferlay et al (2001), which are summarised in Table A.4.9. As it is possible to see, Europe presents high incidence rates (even higher than those for Northern America). However, the deaths to new cases ratio is about 45 percent for Africa, about 38 percent for Asia, about 37 percent for Europe, and just around 25 percent for Northern America (including US and Canada), suggesting high differences with respect to the availability of treatments and prevention tools.

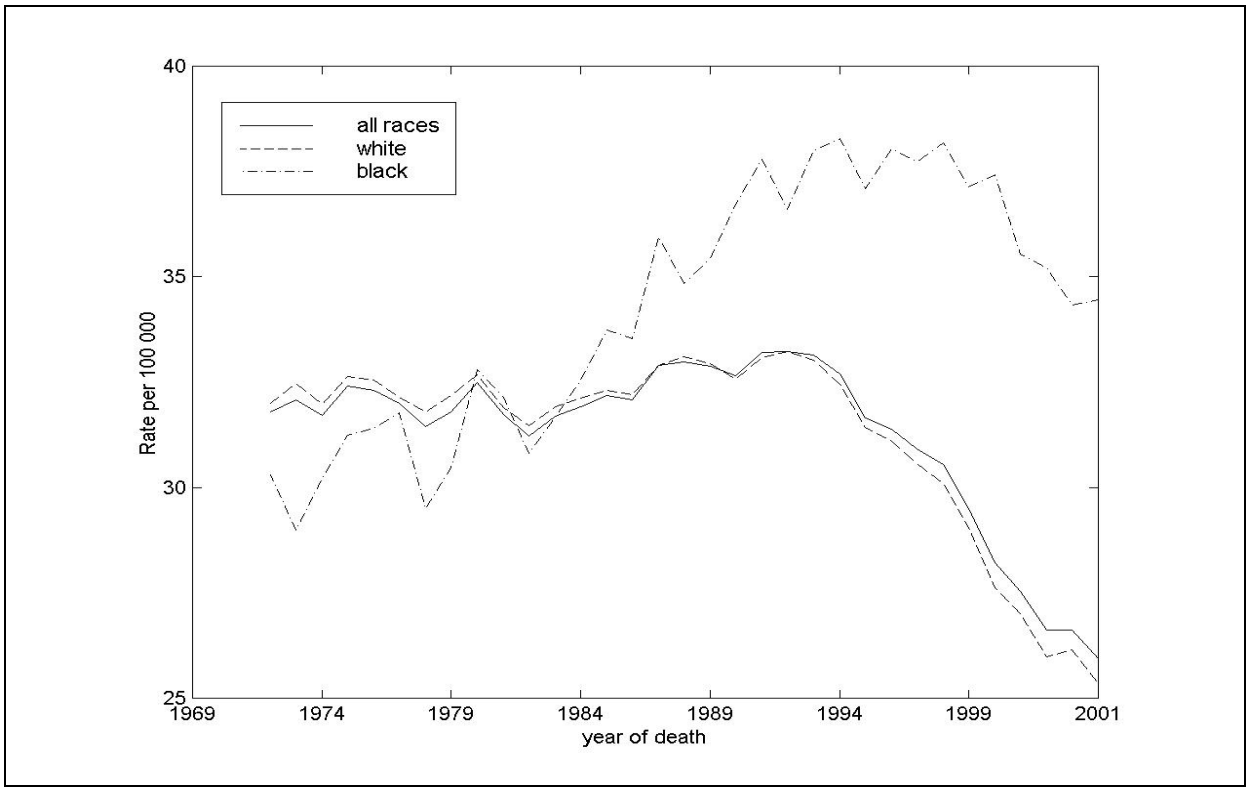
The American Cancer Society (2005) estimates about 211,240 women in the United States will be found to have invasive breast cancer in 2005. About 40,410 women will die from the disease this year.

Figure 12. Age-adjusted incidence rates of breast cancer in US – all ages, 1973–2001



Source: SEER (2004).

Figure 13. Age-adjusted mortality rates for breast cancer in US – all ages, 1969–2001



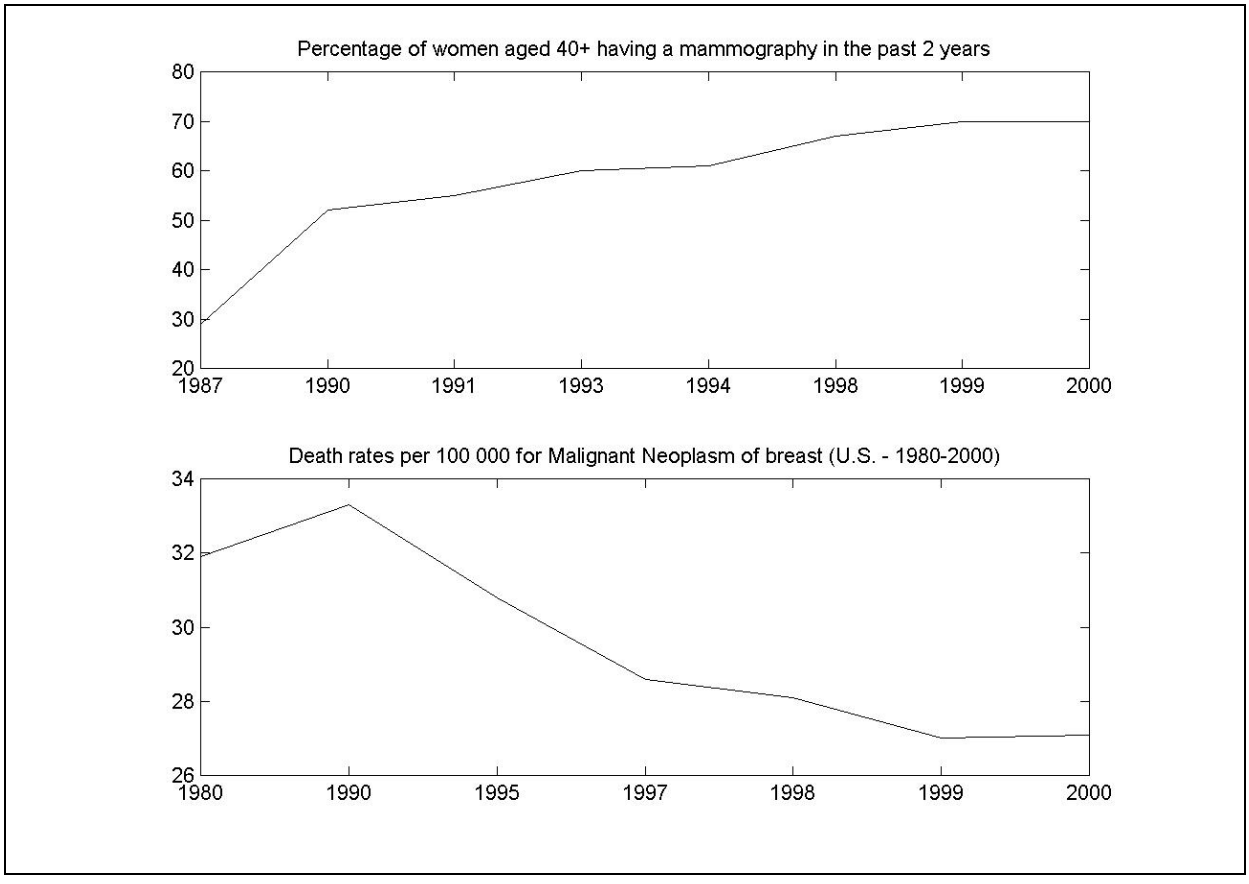
Source: SEER (2004).

As for the economic burden, Wendy (2003) performed a study focusing on the total cost of breast cancer in California. Preliminary estimates of the annual direct costs of breast cancer have been completed for 2000: 12,579 women were discharged from California hospitals with a principal diagnosis of breast cancer, and hospitalisation costs were estimated around $80 million, or an average of $6,346 per discharge.

One third of the hospitalised women were aged 50-64, and 41 percent were over 65. Hospitalisation costs associated with a secondary diagnosis of breast cancer added $28 million in cost. Total healthcare costs, including hospitalisations, physician services, medications, nursing home care, home healthcare, and emergency department visits were then estimated as $284 million.

In Italy, the social cost of BC has been estimated to be over €1 million a year (Italian Society for Cancer Research, AIRC, 2004), whereas Remak and Brazil (2004) estimated the total population cost of metastatic breast cancer around £26 million.

Figure 14. Use of mammography for women older than 40 years and death rates for malignant neoplasm of breasts (US population)



Source: our elaborations of data from Center for Disease Control (CDC, 2004).

c. Background to innovation: history, previous standards and technologies

Only fifty years ago, no established tool was available for the detection of breast cancer at an early stage. However, a singular combination of advances in technology, policy recommendations and legal mandates has fostered massive changes in this situation.

Table A.4.10 presents a summary of the main historical changes in breast screening in the last century. The first attempts to produce a methodology for breast screening date back to the beginning of the 1900s. However, mammography did not begin to emerge until the 1960s, when higher quality image producing methods were made available.

Screening techniques (up to date X-ray mammography is the most used), are based on three distinct stages. The first one is the identification of abnormalities in breast tissue. This can be achieved either by physical examination, or by imaging technique. In general, physical examination is perceived as a less effective method; however, even the most advanced imaging devices are not error free, as will be discussed in the following.

The second stage is that of diagnosis of the identified abnormality, as benign or malignant, by using either other imaging devices, or biopsy procedures. The choice is highly dependent on the conditions of the abnormality, as biopsy is a highly invasive operation.

Finally, abnormalities labelled as malignant must be further investigated, by means of biochemical procedures, and staged according to tumour size and the extent of invasion, and metastasis to determine a prognosis and an appropriate treatment.

X-ray mammographies have produced great advances in the detection of BC: in randomised clinical trials, it has been proved that screening reduced BC mortality by about 25-30 percent in women aged 50 to 70, and about 18 percent in women aged 40-50. However, some concerns remain about standard mammography procedures.

The main inefficiencies of mammography are related to the specificity and sensitivity[18] of the device. In fact, the level of false positive and false negative[19] does represent a major issue, especially in a complicated area such as cancer.

False positive results have an impact both on the clinical and the economic point of view. In fact, in case of a positive test, a woman is typically further investigated, possibly by means of invasive procedures, which lead to *a)* impairment in the patient's quality of life (Lerman et al, 1991), and *b)* additional costs for second stage investigations and overtreatments that could be avoided.

As for false negatives, their impact is clearly huge, and affects mostly the clinical level. Moreover, because of the potential dire consequences associated with false negative findings, the number of lawsuits for medical malpractice stemming from missed cancer diagnoses considerably increased, since the massive introduction of screening programs.

d. Innovation: description, impact on health and on costs

Conventional X-ray mammography is nowadays a mature technology, widely used. However, as reported above, standard film-based mammography can be associated with bias in results,

[18] The *sensitivity* of a device is defined as the ability of a test to correctly identify patients with the investigated disease, whereas by the term *specificity* we refer to the ability of a test to correctly identify patients without the investigated disease.

[19] A *false positive* is a patient who has not the disease, but is positively diagnosed by the test, whereas a *false negative* is a patient for which the test does not identify the presence of the disease, even if it is actually present.

and may not provide adequate diagnostic information for some categories of patients, i.e. women with radiosense breast tissue.

The Institute of Medicine – National Research Council (2001) report standard mammography misses about 15 percent of breast cancer lesions, and that 60 to 85 percent of the lesions detected by mammography are benign, and thus many biopsies could be potentially avoided.

The current limitations of mammography devices have been driving continuous innovation processes, aimed at developing new methods for the detection of BC. Among them, the most relevant are digital mammography, computer-aided detection and diagnosis (CAD) devices, ultrasound devices, and Magnetic Resonance Imaging (MRI).

Although different in nature and in the technologies used (see Table A.4.1), these new tools share some common features. In fact, all of them derive from the need of reducing the biases of standard mammography devices, in terms of specificity and sensitivity. In addition, all of these devices can be used jointly with mammography, in order to provide a better estimation and to avoid useless interventions.

Several economic evaluations have been performed recently. Gold et al (1996) report that the cost per years of life gained using mammography is within the threshold of $50,000/QALY, which is perceived as a reasonable range. However, other studies, such as that of Rosenquist and Lindfors (1998) suggest high variability in the results, depending on age, screening interval, and the assumed effectiveness or benefit measure, typically a given percentage decrease in BC mortality.

Other comparisons have been performed between standard mammography and the newer technologies: for instance, digital mammography was compared to film screen devices; so far, the cost of new machines is significantly higher (about $450,000 per unit, as compared with about $70,000 per standard mammography device). In addition, the real improvements in specificity and sensitivity have not been fully explored. A simulation study conducted by Nields and Galaty (1998) showed that even a low increase of the devices predictive capability (number of BC accurately detected) of about 2 percent could turn to produce savings, due to the reduced number of unnecessary follow-up biopsies.

Due to the lack of substantial data sets linking the newer BC detection devices and the alleged reduction in BC mortality rates (Institute of Medicine – National Research Council, 2001), some simulation studies have also analysed the economic impacts of MRI. A major result was that this technology could turn out to be to be particularly effective, and cost-effective especially within young women (Plevritis, 2000). However, although these results can provide useful information for policy makers, they suffer from being inadequate in terms of coverage perspective, not being based on clinical trials.

Conclusions

Breast cancer screening is somehow an archetypical topic in the health technology assessment field. In fact, several pieces of evidence show that the patients can benefit from these procedures, although concerns remain due to: *a)* the fact that screening is not *per se* a life saving procedure; and *b)* the high costs associated.

The potentiality of BC screening devices has always been high, as this industry is linked to high-tech counterparts (i.e. some newly researched devices are partly funded by institutions such as Military Departments).

However, further and more up-to-date investigations are needed in order to assess the actual effectiveness, and more specifically the actual cost-effectiveness of these innovations. The increase of the overall costs associated with the pathology can be attributed to the highly innovative nature of the industry, besides the high prevalence.

5. COMPETITIVENESS, PRODUCTIVITY AND INDUSTRY STRUCTURE

Summary of the chapter

In this chapter we provide descriptive evidence of the level of competitiveness of the European medical device industry in comparison with the industry in the US and in Japan. Competitiveness is a complex concept and different indicators have been considered in this Study, ranging from measures of value added and productivity, to trade analysis and industry structure indicators.

The data presented in this chapter show that the European industry is lagging behind the US industry, both in terms of production capabilities and international competitiveness. This result also holds when analysing the R&D side of the industry (see Chapter 6).

The European medical device industry is extremely heterogeneous both across sub-markets and countries that show different levels of production, value added, and outcomes in terms of productivity and international trade.

Even though the analysis of product flows between countries shows the leading role of the US on the international scene, European countries have a competitive position in most of the diagnostic equipment segment of the industry.

The analysis of the structure of the industry reveals that European firms are smaller and less diversified than US counterparts, a pattern which is likely to have implications in terms of minor resources and funding for research activities.

5.1 Introduction and methodology

This chapter presents indicators of market structure and dynamics for the medical device sector. The analysis will be performed at two different levels of aggregation:

- at a national level, an assessment of the performance and characteristics of the industry will be used to characterise the main worldwide producers, and to compare, at the macro level, the performance of different countries. Data for the analysis are drawn from different sources[20]. Different data sources employ different classifications and definitions; therefore particular care has to be paid in the international comparison of national trends and performances.
- at a more disaggregated level, we have employed data from the US Food and Drug Administration (FDA), containing fine-grained information about registered companies and medical device products, to characterise the industry at the micro level. We focused on the structure of the industry, particularly in relation to the level of competition and corporate diversification, both across sub-markets and geographical boundaries. In order to get a comprehensive picture, the analysis in the next chapter will take into consideration the processes and characteristics of technological innovation in medical devices.

[20] For the EU data are from Eurostat; for the US from: US Census, AdvaMed and the US International Trade Commission; for Japan from the Ministry of Health, Labor and Welfare of Japan.

It is important to point out that the extent of the analysis performed here has been determined by data availability and quality and international comparisons are severely undermined due to lack of data uniformity at an international level.

5.2 Productivity indicators and snapshot of the industry

In this Section, we perform a comparative analysis of trends and patterns of the EU medical device industry with respect to the industry in the US and in Japan. A number of indicators and variables will be reviewed. The medical device industry is highly heterogeneous both across countries and at the sub-market level. When data are available, we will perform the analysis at the sub-market level and at Member State level in order to account for this heterogeneity.

Box 1: Data comparability issues – production, employment and value added

The analysis presented in this section has been based on various sources. For EU Member States, data have been collected from the Eurostat NewCronos database (Eurostat, 2004a). We considered the NACE 33.1 category, which reports data regarding the "Manufacture of medical and surgical equipment and orthopaedic appliances". This class includes the manufacture of instruments and appliances used for medical, surgical, dental or veterinary purposes, manufacture of syringes, needles used in medicine, mirrors, reflectors, endoscopes, etc., manufacture of medical, surgical, dental or veterinary furniture, and manufacture of orthopaedic appliances.

Data for Japan are based on data published by the Ministry of Health, Labour and Welfare (MHLW), and they have been obtained trough the Japanese Federation of Medical Device Associations (JFMDA).

For the US, various data sources have been accessed, including AdvaMed and the US Census Bureau. For the US census data relevant NAICS sectors have been summed up: In-Vitro Diagnostic Substance Manufacturing (NAICS 325413); Laboratory Apparatus and Furniture Manufacturing (NAICS 339111); Surgical and Medical Instrument Manufacturing (NAICS 339112); Surgical Appliance and Supplies Manufacturing (NAICS 339113); Dental Equipment and Supplies Manufacturing (NAICS 339114); Ophthalmic Goods Manufacturing (NAICS 339115); Electromedical and Electrotherapeutic Apparatus Manufacturing (NAICS 334510); Irradiation Apparatus Manufacturing (NAICS 334517).

One major difference between the aggregate for the EU on the one side, and the US and Japan on the other is the inclusion in the latter two of in vitro diagnostics (IVD). NACE 33.1 does not include in vitro diagnostics, which are instead included in other classes (i.e. NACE 24.4 "Manufacture of pharmaceutical preparations" and 24.6 "Manufacture of other chemical products").

When data allows, we will present figures for the US both considering and excluding the NAICS 325413 (IVD).

Chapter 7 provides a more detailed description of available data sources and their shortcomings.

a. Production, employment and productivity

We start by exploring the macro-dynamics at work in this industry by looking at the value of production and value added in the EU, US and Japan.

Tables 1 and 2 report, respectively, the value of production and value added together with the share in total manufacturing.

The US is the top producer in the medical device industry at a worldwide level. The production in the EU is roughly half[21] that of the US. Japan is the third world producer. Medical device production is on the rise at the global and national level. In particular, production in the new Member States has increased steadily from 1999 to 2002.

Table 1. Medical device real production value (constant 1995 € million), and share of production value in manufacturing total

Country	1997	1998	1999	2000	2001	2002	2002
	€	€	€	€	€	€	%
US	48112	50220	52886	54698	55002	52100	2.0
Japan	12368	12444	12363	12597	13057	13118	0.5
EU-25	n.a.	n.a.	n.a.	29155	32139	33803	0.8
EU-15	n.a.	n.a.	29228	28212	31059	n.a.	1.1
New Member States	n.a.	n.a.	510	561	614	705	0.3

Source: AdvaMed (2004); MHLW (2004); Eurostat (2004a; see Table A.5.1 for details about data availability for EU Member States); OECD (2004; for total manufacturing in Japan and in the US).

Note: for data and aggregates definition see Box 1.

High heterogeneity exists across Member States (see Table A.5.1 in the Annex): for 2001, the share of medical device production over total manufacturing ranges from 0.1 percent (Portugal) to 3.8 percent (Ireland). As for Ireland, this figure has more than doubled from 1997 to the year 2001 and it is still increasing in the year 2002 peaking 4.1 percent of total manufacturing production. Germany is the top medical device producer in Europe, followed by France, Italy, Ireland, and the UK.

A similar pattern emerges from data on value added.

[21] Aggregates for the EU have been obtained as the sum of available data; some data are missing for a few Member States, see Table A.5.1 in the Annex.

Table 2. Medical device value added at factor cost (constant 1995 € millions), and share of value added in manufacturing total

Country	1997	1998	1999	2000	2001	2002	2002
	€	€	€	€	€	€	%
US	31778	33790	35257	36776	37625	38911	3.1
US (excl. IVD)	27163	29201	30188	31590	32197	35246	2.8
Japan	14729	14838	14467	14706	14779	n.a.	1.6
EU-25	n.a.	n.a.	n.a.	13937	14709	n.a	n.a
EU-15	n.a.	n.a.	14606	13527	14255	12739	1.5
New Member States	n.a.	n.a.	n.a.	228	271	305	0.6

Source: US Census (2004); MHLW (2004); Eurostat (2004a; see Table A.5.2 for details about data availability for EU Member States); OECD (2004; for total manufacturing in Japan and in the US).
Note: for data and aggregates definitions see Box 1. Data for Japan are for NACE 33 ("Medical, precision and optical instruments, watches and clocks")

Table 3 reports the number of employees, and share of employment with respect to the whole manufacturing sector. The number of employees in the industry is roughly the same for the EU and the US.

Table 3. Number of employees (thousands) in medical devices and share medical device employment in total manufacturing

Country	1997	1998	1999	2000	2001	2002	2002
	n.	n.	n.	n.	n.	n.	%
US	341	354	352	351	353	373	2.4
US (excl. IVD)	302	314	311	311	312	346	2.2
Japan	239	234	223	213	213	n.a.	1.9
EU-25	n.a.	n.a.	326	333	352	n.a.	1.2
EU-15	n.a.	n.a.	299	304	319	n.a.	1.3
New Member States	n.a.	27	27	28	32	35	1.1

Source: US Census (2004); MHLW (2004); Eurostat (2004a; see Table A.5.3 for details about data availability for EU Member States); OECD (2004; for total manufacturing in Japan and in the US).
Note: for data and aggregates definitions see Box 1. Data for Japan are for NACE 33 ("Medical, precision and optical instruments, watches and clocks")

Consistently with the findings about value added and production, the number of employees in Germany is the highest among EU Countries, and has increased over the period 1991-2001. However, in the year 2002, the number of employees in this country has significantly decreased (see Table A.5.3). Notwithstanding this slowdown in production, the share over the total employment is higher in this Country than the EU-15 average, which equals 1.6 percent in 2002. Ireland is the Country where the share of employment in manufacturing is the highest (6.3 percent) and the number of employees has significantly increased over the period. Where

available, the data for the share of employment over total manufacturing point to a share for the new Member States that is always lower than the EU-15 average.

A similar number of employees together with large differences in value added between the EU and the US are reflected in different value added per employees, a proxy for labour productivity (see Table 4).

Table 4. Medical device real gross value added per person employed (apparent labour productivity) (1995 € thousands)

Country	1997	1998	1999	2000	2001	2002
US	93,2	95,5	100,2	104,8	106,6	104,3
Japan	61,6	63,4	64,9	69,0	69,4	n.a.
EU-25	n.a.	n.a.	n.a.	36,8	36,6	n.a.
EU-15	36,4	35,8	39,1	41,7	40,5	n.a.
New Member States	n.a.	n.a.	n.a.	9,1	5,5	

Source: Eurostat (2004a); US Census (2004); OECD (2003).

Note: for data and aggregates definitions see Box 1. Data for Japan are for NACE 33 ("Medical, precision and optical instruments, watches and clocks")

Apparent labour productivity for the EU is significantly lower than for the US and Japan. The figures show an upward trend for all areas, but while for the EU (EU-15) between 1997 and 2001 it has increased by 10 percent, in the US the increase has been 15 percent, and in Japan 12 percent.

Denmark, France, and Ireland represent exceptions to the general trend in Europe (see Table A.5.4). The Irish industry has witnessed a sharp increase in labour productivity over the period 1998-2002 (+73,2 percent), and, since 1999, it has registered the highest value added per person employed among the European countries.

b. Trade flows

Taking a different perspective, the assessment of the competitive position of the EU, Japan, and the US can be made by looking at the trade flows of medical device products. Here, the analysis focuses on the import and export of products. In the next chapter we will also take into consideration the international flow of technologies within the medical device industry. The analysis of these two patterns will allow for identifying the competitive position of the European countries, the US and Japan in the medical device industry both in terms of products and technologies.

Box 2: Data comparability issues – trade flows

The analysis is based on the Eurostat ComExt Database and on the Trade Database of the US International Trade Commission, that record the amount, source, and destination of trade flows. The two data sources employ different classification systems. Eurostat uses the "Combined Nomenclature" (CN), while the US International Trade Commission database employs the "Harmonised Tariff Schedule" (HTS). However the two classification systems can be matched at the six-digit level that is the level of aggregation that is employed in this analysis.

In order to be consistent with the analysis presented at the beginning of this section, the aggregate used for the analysis has been composed in harmony with the NACE 33.1 class (see Box 1 and Chapter 7 for details). The six-digit level of disaggregation has been considered in the analysis, as reported in the table. The table also reports the codes that will be employed in the figures that follow. The first digit of each code groups the products into product classes: diagnostic equipment (d), other electronic devices (e), disposables (x), dental devices (t), ophthalmic (o), mechano-therapy (m); implantable high-tech devices (h), other implantables (i), furniture (f), apparatus for other uses (u).

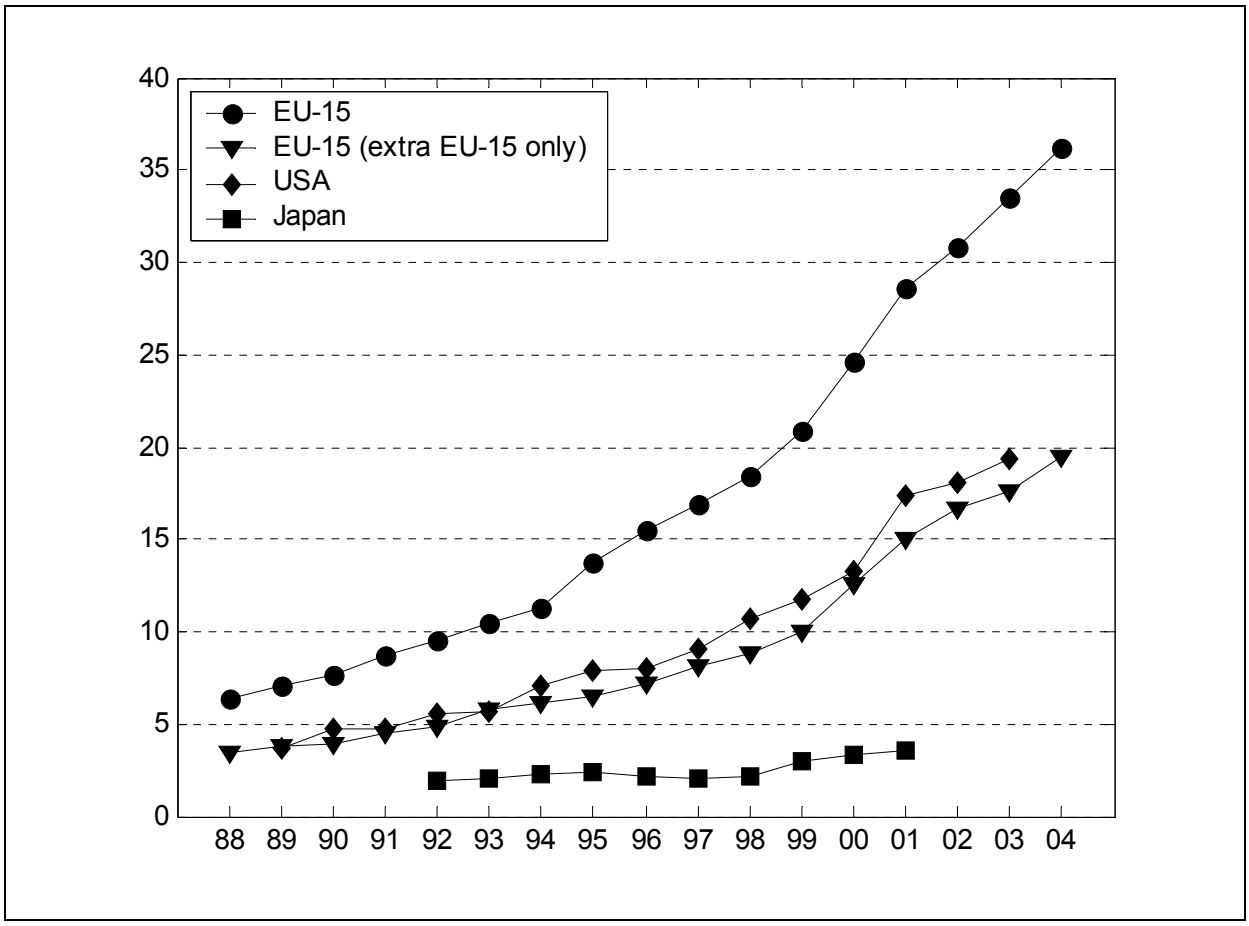
Sub-markets considered in the international trade flows analysis

Code	CN/HTS	Description
d0	902290	X-ray generators other than x-ray tubes, high tension generators, control panels and desks, screens, examination or treatment tables, chairs and the like, and general parts and accessories for apparatus of heading 9022, n.e.s.
d1	901812	Ultrasonic scanning apparatus
d2	901813	Magnetic resonance imaging apparatus
d3	901814	Scintigraphic apparatus
d4	901820	Ultra-violet or infra-red apparatus used in medical, surgical, dental or veterinary sciences
d5	902212	Computer tomography apparatus
d6	902213	Apparatus based on the use of x-rays for dental uses
d7	902214	Apparatus based on the use of x-rays, for medical, surgical or veterinary uses (excluding for dental purposes and computer tomography apparatus)
d8	902221	Apparatus based on the use of alpha, beta, or gamma radiation for medical, surgical, dental or veterinary uses
d9	902230	X-ray tubes
e1	901811	Electro-cardiographs
e2	901819	Electro-diagnostic apparatus, including apparatus for functional exploratory examination or for checking physiological parameters (excluding electro-cardiographs)
e3	901890	Instruments and appliances used in medical, surgical, dental or veterinary sciences n.e.s.
f1	940210	Dentists', barbers' or similar chairs and parts thereof
f2	940290	Other furniture
h1	902111/ 902131	Artificial joints, for orthopaedic purposes
h2	902150	Pacemakers for stimulating heart muscles (excluding parts and accessories)
i1	902119/ 902110	Orthopaedic appliances and fracture appliances (excluding artificial joints)
i2	902130/ 902139	Artificial parts of the body (excluding artificial teeth)
i3	902140	Hearing aids (excluding parts and accessories)
i4	902190	Articles and appliances, which are worn or carried, or implanted in the body, to compensate for a defect or disability (excluding artificial parts of the body, complete hearing aids and complete pacemakers for stimulating heart muscles)
m1	901910	Mechano-therapy appliances, massage apparatus and psychological aptitude-testing apparatus
m2	901920	Ozone therapy, oxygen therapy, aerosol therapy, artificial respiration or other therapeutic respiration apparatus
o1	901850	Ophthalmic instruments and appliances n.e.s.

Code	CN/HTS	Description
t1	901841	Dental drill engines, whether or not combined on a single base with other dental equipment
t2	901849	Instruments and appliances used in dental sciences n.e.s.
t3	902121	Artificial teeth
t4	902129	Dental fittings (excluding artificial teeth)
x1	901831	Syringes, whether or not with needles, used in medical, surgical, dental or veterinary sciences
x2	901832	Tubular metal needles and needles for sutures, used in medical, surgical, dental or veterinary sciences
x3	901839	Needles, catheters, cannulae and the like, used in medical, surgical, dental or veterinary sciences (excluding syringes, tubular metal needles and needles for sutures)
u1	902219	Apparatus based on the use of x-rays for other uses
u2	902229	Apparatus based on the use of alpha, beta, or gamma radiations, for other uses

First, we considered the medical device aggregate obtained as the sum of the subclasses listed in the table in Box 1. Trends in the total exports, imports, and "trade balance" are presented in Figures 1-3.

Figure 1. Total exports, medical devices, EU-15, US, Japan, 1988-2004, € billion

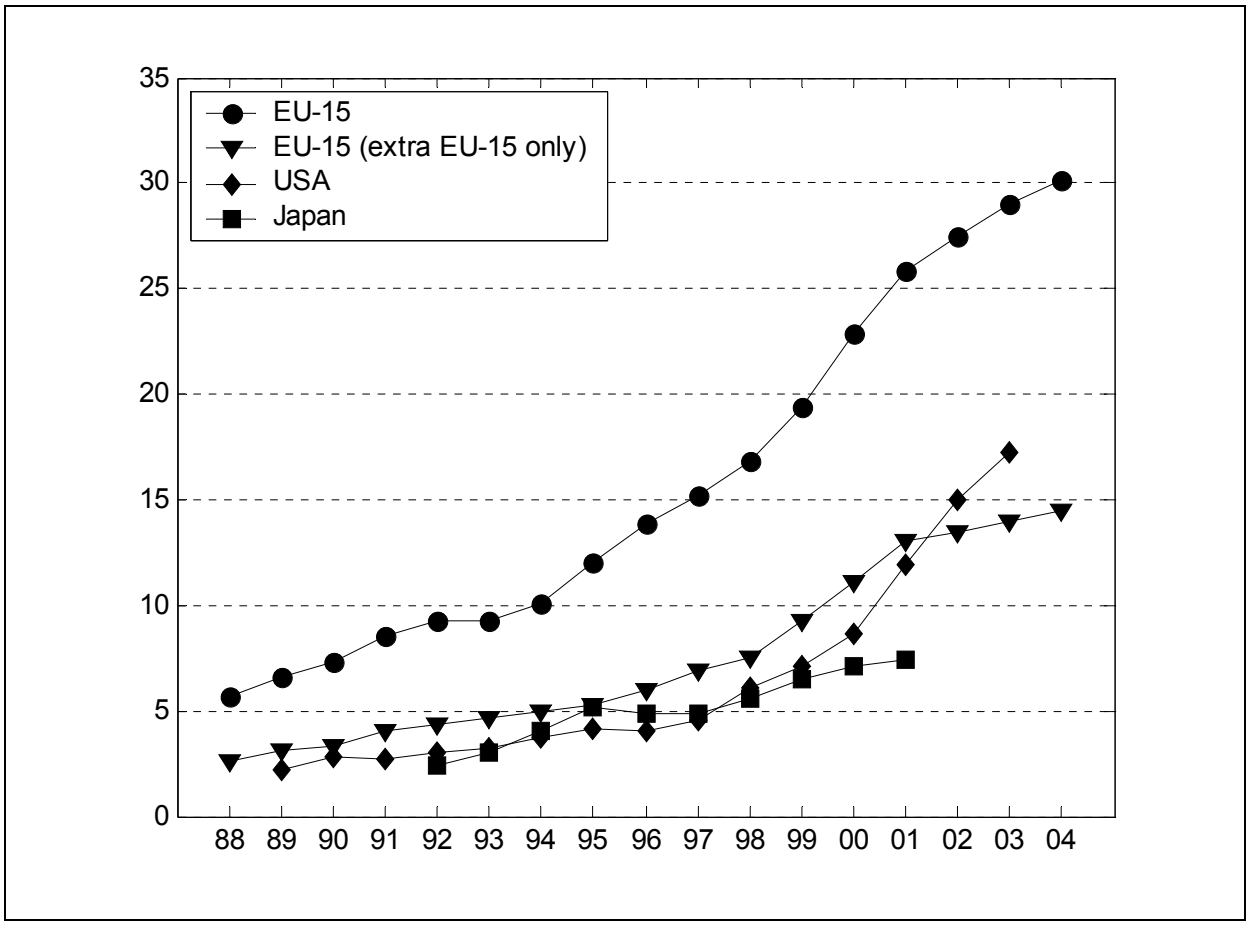


Source: Eurostat (2004b), US International Trade Commission (2004), MWLH (2003).

An upward trend characterises the total exports of the EU[22] and of the US, while Japan is characterised by lower and stable dynamics. Total exports from the EU are higher than exports from the US. However, when considering only extra EU-15 exports, the value for the US and Europe are much more similar.

On the other side, if we look at total imports, Japanese, extra EU-15 and US values are similar and show similar patterns (see Figure 2).

Figure 2. Total Import, medical devices, EU-15, US, Japan, 1988-2004, € billion



Source: Eurostat (2004b), US International Trade Commission (2004), MWLH (2003).

An important impetus to intra-EU trade is believed to have come from the 1993 European Directive on Medical Devices, which set out the classification criteria for medical devices and outlined the appropriate conformity assessment procedures for each class of device at a European level.

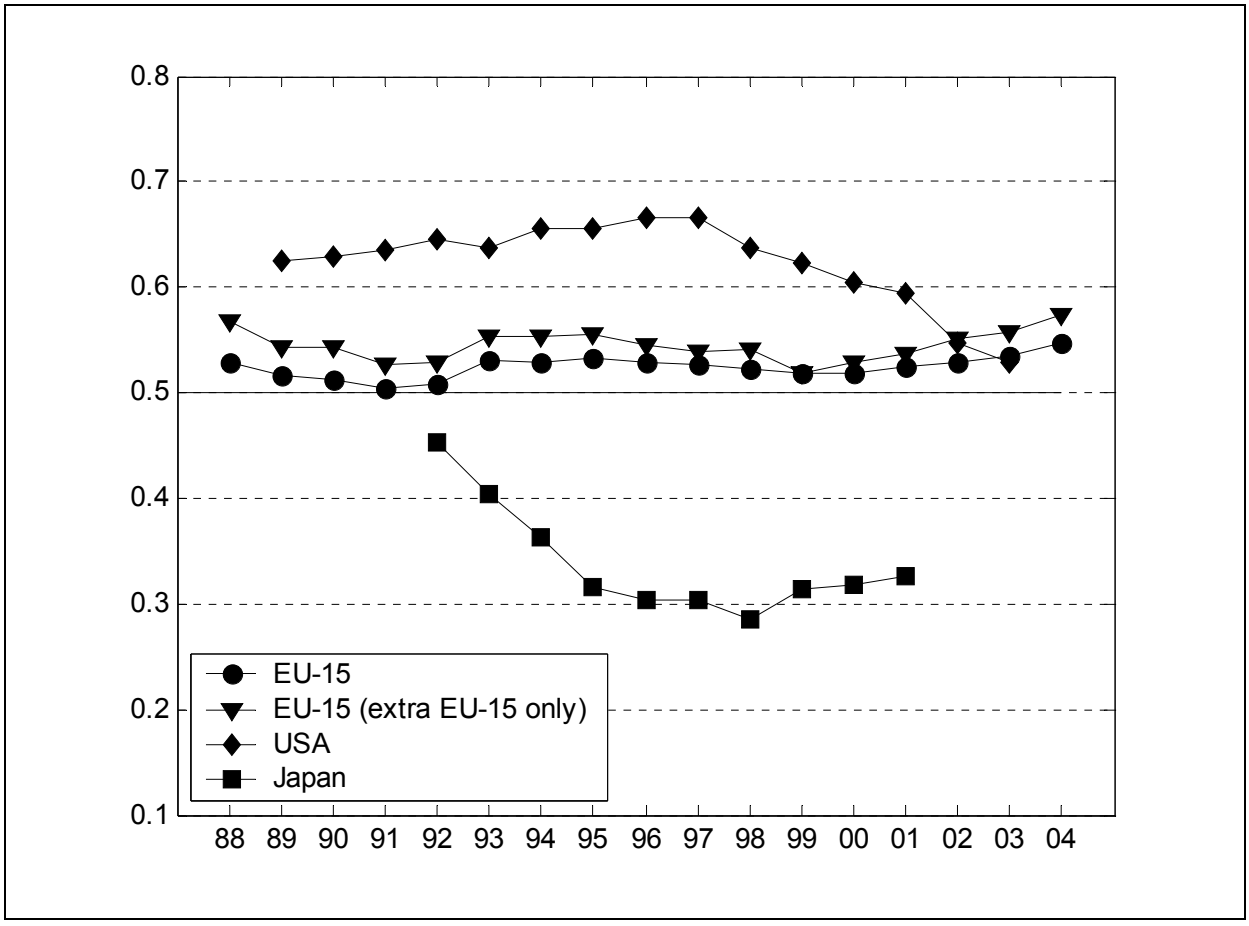
In order to measure the trade balance, we computed the share of exports over the total trade (the sum of imports and exports). This index ranges from 0 (the country only imports) to 1

[22] Total exports for the EU are the sum of intra and extra EU trade; Extra-EU figures do not include intra-EU trade.

(the country only exports) and it equals 0.5 in case the value of imports is the same of the value of exports[23].

Japan is the major net importer of medical devices, and its imports largely exceed exports. The US trade balance for medical devices has been deteriorating in recent years when the value of the index has decreased, pointing to a larger increase of imports with respect to exports. The trade balance for the EU does not show any particular trend, and the medical device industry gives a positive contribution to the European trade balance (see Figure 3).

Figure 3. "Trade Balance" (ratio of export over total trade), EU-15, US, Japan, 1988-2004

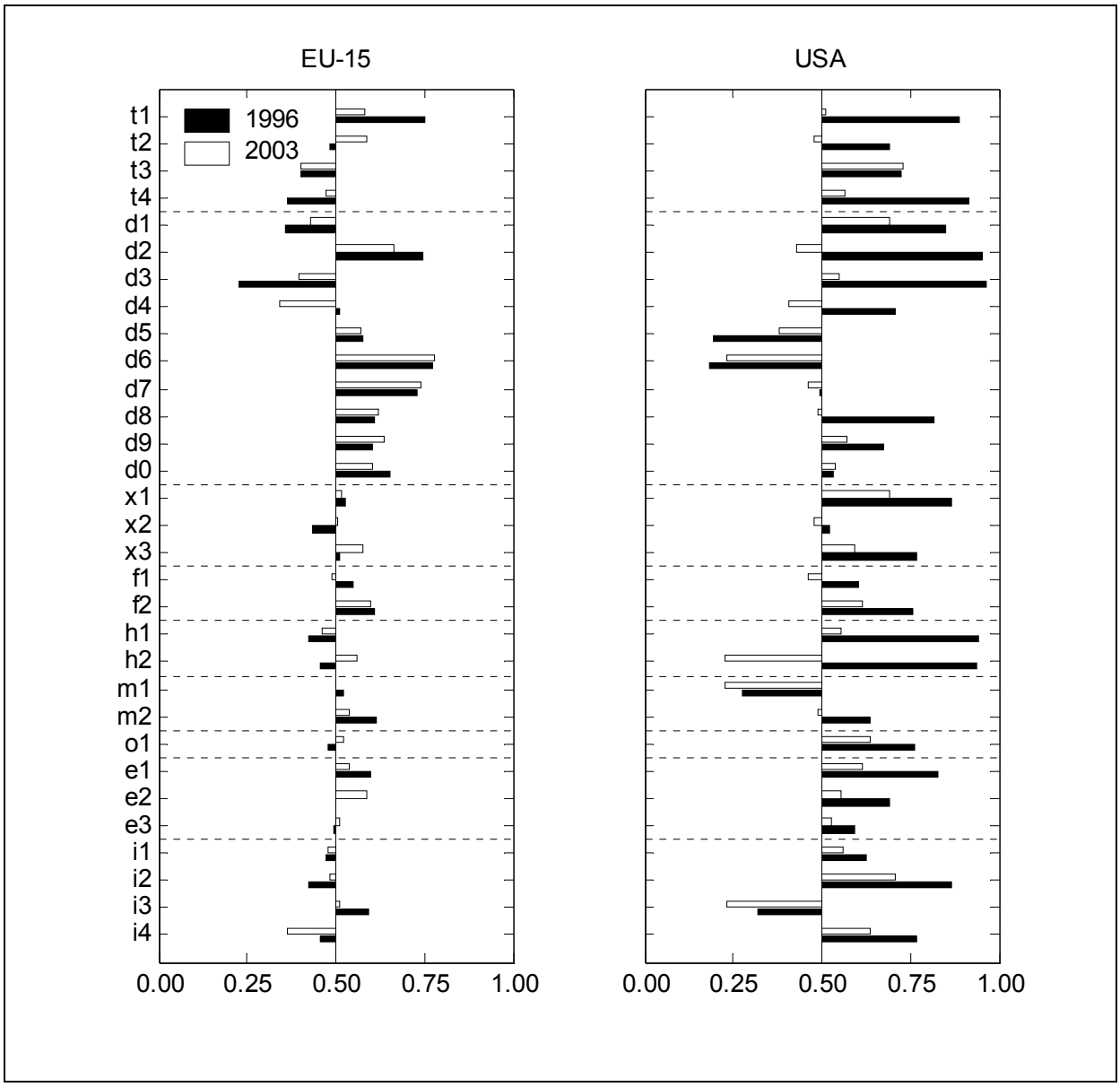


Source: Eurostat (2004b), US International Trade Commission (2004), MWLH (2003).

Next, we move to a more disaggregated level, and consider data at the submarket level, following the classes presented in Box 2. The analysis can show in which sub-markets EU and US are net exporters or importers, and the magnitude of this phenomenon. Figure 4 gives a graphical representation of the index of "Trade Balance" in the years 1996 and 2003, while Table 5 summarises its magnitude and direction.

[23] Trade balance is normally defined as the difference or the ratio of imports and exports. A different index was introduced here to be use in the following correspondence analysis.

Figure 4. "Trade Balance" (ratio of export over total trade), at the sub-market level, EU-15, US, 1996, 2003



Source: Eurostat (2004b), US International Trade Commission (2004).
Note: see Box 2 for the correspondence of the abbreviations.

Table 5. Direction and magnitude of the "Trade Balance", at the sub-market level, EU-15, US, 1996, 2003

Code	Description	EU-15		US	
		1996	2003	1996	2003
	diagnostic equipment				
d0	X-ray generators other than x-ray tubes, high tension generators, control panels and desks, screens, examination or treatment tables, chairs and the like, and general parts and accessories for apparatus of heading 9022, n.e.s.	+	+	+	+
d1	Ultrasonic scanning apparatus	-	-	++	+
d2	Magnetic resonance imaging apparatus	+	+	++	-
d3	Scintigraphic apparatus	--	-	++	+
d4	Ultra-violet or infra-red apparatus used in medical, surgical, dental or veterinary sciences	+	-	+	-
d5	Computer tomography apparatus	+	+	--	-
d6	Apparatus based on the use of x-rays for dental uses	++	++	--	--
d7	Apparatus based on the use of x-rays, for medical, surgical or veterinary uses (excl. for dental purposes and computer tomography apparatus)	+	+	-	-
d8	Apparatus based on the use of alpha, beta, or gamma radiations, for medical, surgical, dental or veterinary uses	+	+	++	-
d9	X-ray tubes	+	+	+	+
	other electronic device				
e1	Electro-cardiographs	+	+	++	+
e2	Electro-diagnostic apparatus, incl. apparatus for functional exploratory examination or for checking physiological parameters (excl. electro-cardiographs)	+	+	+	+
e3	Instruments and appliances used in medical, surgical, dental or veterinary sciences n.e.s.	-	+	+	+
	forniture				
f1	Dentists', barbers' or similar chairs and parts thereof	+	-	+	-
f2	other	+	+	++	+
	implantable high tech				
h1	Artificial joints, for orthopaedic purposes	-	-	++	+
h2	Pacemakers for stimulating heart muscles (excl. parts and accessories)	-	+	++	--
	other implantable				
i1	Orthopaedic appliances and fracture appliances (excl. artificial joints)	-	-	+	+
i2	Artificial parts of the body (excl. artificial teeth)	-	-	++	+
i3	Hearing aids (excl. parts and accessories)	+	+	-	--
i4	Articles and appliances, which are worn or carried, or implanted in the body, to compensate for a defect or disability (excl. artificial parts of the body, complete hearing aids and complete pacemakers for stimulating heart muscles)	-	-	++	+
	mechano-therapy				
m1	Mechano-therapy appliances, massage apparatus and psychological aptitude-testing apparatus	+	+	-	--
m2	Ozone therapy, oxygen therapy, aerosol therapy, artificial respiration or other therapeutic respiration apparatus	+	+	+	-
	ophthalmic				
o1	Ophthalmic instruments and appliances n.e.s.	-	+	++	+
	dental				
t1	Dental drill engines, whether or not combined on a single base with other dental equipment	++	+	++	+
t2	Instruments and appliances used in dental sciences n.e.s.	-	+	+	-
t3	Artificial teeth	-	-	+	+

Code	Description	EU-15		US	
		1996	2003	1996	2003
t4	Dental fittings (excl. artificial teeth)	-	-	++	+
	disposable				
x1	Syringes, whether or not with needles, used in medical, surgical, dental or veterinary sciences	+	+	++	+
x2	Tubular metal needles and needles for sutures, used in medical, surgical, dental or veterinary sciences	-	+	+	-
x3	Needles, catheters, cannulae and the like, used in medical, surgical, dental or veterinary sciences (excl. syringes, tubular metal needles and needles for sutures)	+	+	++	+

Legend:

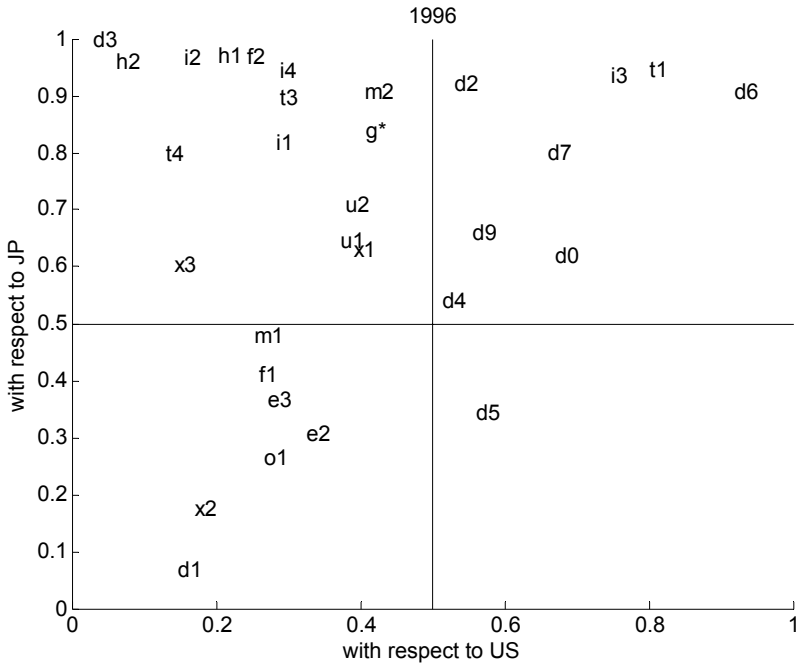
- \- value of the index <0.25
- -- value of the index ≥0.25 and <0.50
- \+ value of the index >0.50 and <0.75
- ++ value of the index ≥0.75

Dental and high-tech implantable devices are sub-markets where the US is a major net exporter, while the global position of the EU countries is weaker. This is also the case of other implantable and electronic devices. As for the diagnostic equipment segment (d), with few exceptions (ultrasonic scanning apparatus and scintigraphic apparatus) the European countries are major net exporters. In the ultraviolet or infrared apparatus sub-market (d4) the EU has worsened its position becoming a net importer of this kind of devices in 2003.

Figures 5 and 6 focus on the international trade flows between the EU on the one side, and the US and Japan on the other. These are represented for 1996 (Figure 5) and 2003 (Figure 6). EU Trade flows from/to the US and Japan have been calculated separately (and represented in the two axes in the Figures below).

The EU appears as a major net exporter of diagnostic equipment, having a positive trade balance with both the US and Japan: most of the products within the diagnostic equipments category (whose first digit is “d” in the figure) are placed in the top right panel in Figures 5 and 6 (i.e., our measure of “trade balance” is greater than 0.5 in both cases). The exceptions are the sub-market of the ultrasonic scanning apparatus, where the EU has a negative trade balance both with respect to the US and Japan, and scintigraphic apparatus, where the EU is a major importer from the US. In 2003, the EU has become a net exporter of pacemakers (h2) both with respect to the US and Japan.

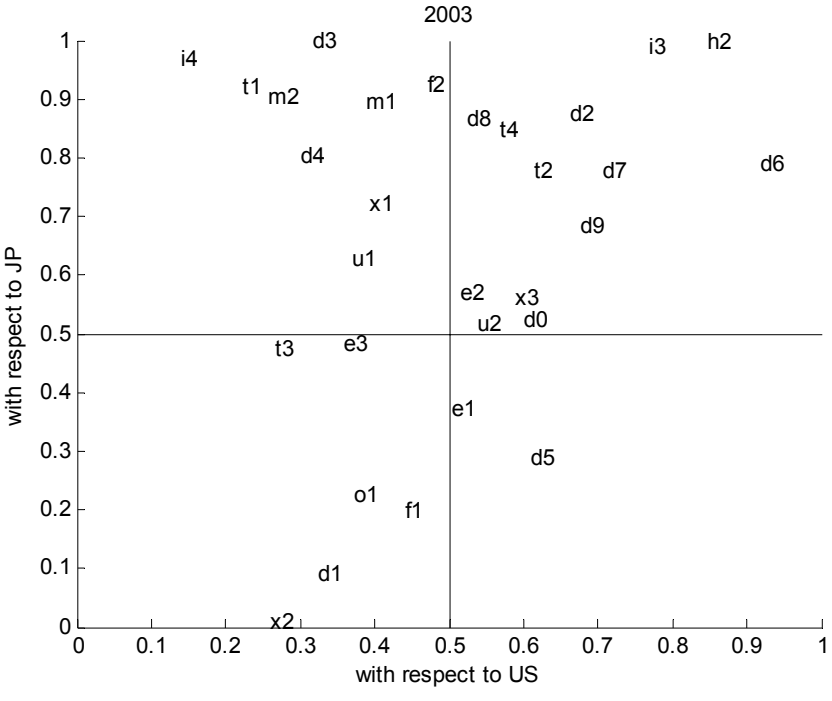
Figure 5. "Trade Balance" (ratio of export over total trade), at the sub-market level, EU-15 with respect to US and Japan, 1996



Note: **g*** comprises d8, e1, and t2

Source: Eurostat (2004b).

Figure 6. "Trade Balance" (ratio of export over total trade), at the sub-market level, EU-15 with respect to US and Japan, 2003



Source: Eurostat (2004b).

Finally, correspondence analysis has been employed to study the pattern of specialisation of country's flows of international trade (see Box 3). This technique has been applied to a matrix containing information about the "trade balance" of each country at the product level. Each row of the matrix is assigned to a product, and each column represents a country. The entries in the matrix report for each country, at the product level, the "trade balance" as measured by the ratio of exports over total trade (imports plus exports).

Box 3: Correspondence Analysis

Correspondence analysis is a statistical methodology that allows the graphic and synthetic analysis and description of large two-dimensional tables by finding the best simultaneous representation of the row and the columns in the table.

It is often applied to contingency tables, i.e. tables in which you find at the intersection of a row and a column the number of units (which might be, for example, individuals or firms) that share the characteristic of the row and that of the column, but it can also be extended to other settings, as is the case in this Study. Only one restriction on the data is necessary for the analysis: the entries in the cells of the table must be non-negative numbers.

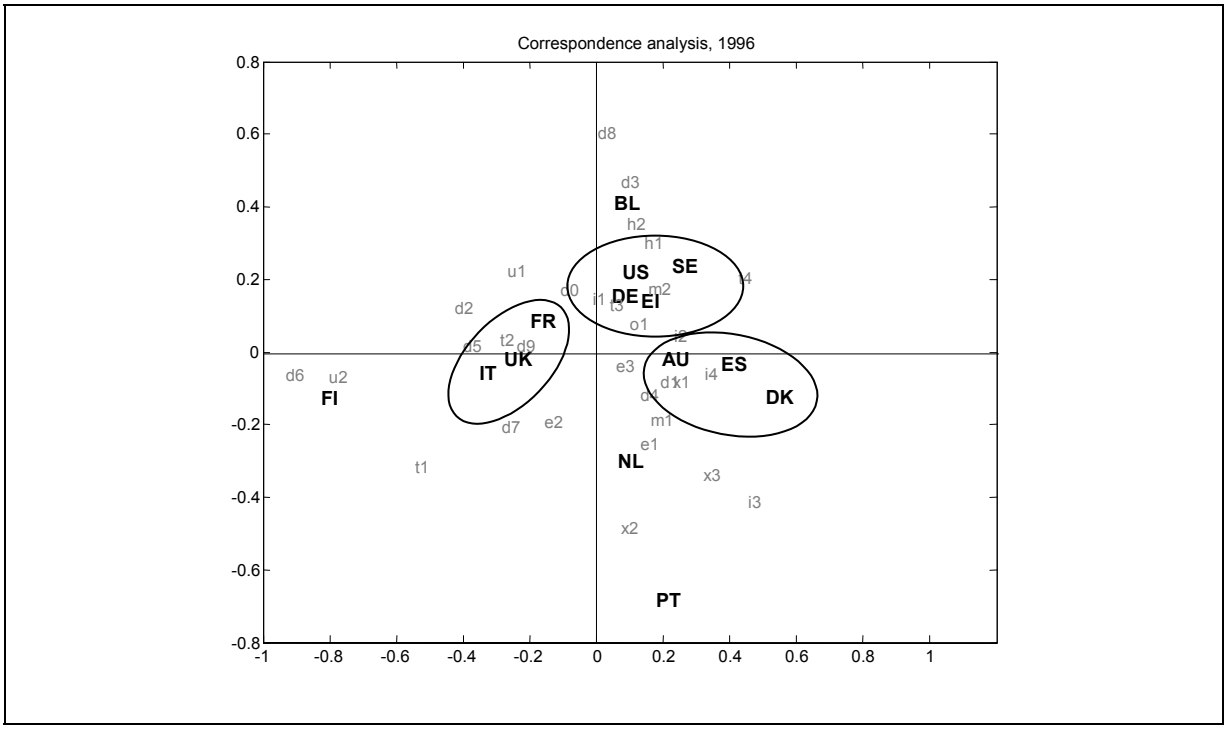
The analysis highlights patterns of similarities among the rows and the columns of the table and allows identifying the existence of relationships between them.

The main output of the analysis, the one that is mostly relevant for this Study, is a graphical representation on a two-dimensional plane, giving a synthetic representation of the structure of the data points, and allowing the comparison with the hypothetical situation of independence between the rows and the columns.

The graph can be interpreted along two dimensions. First the positions relative to an axis of the points belonging to a same group (either row or column data points) give information about the similarities of profiles within each group. Two data points that are close on the graph also have a similar profile.

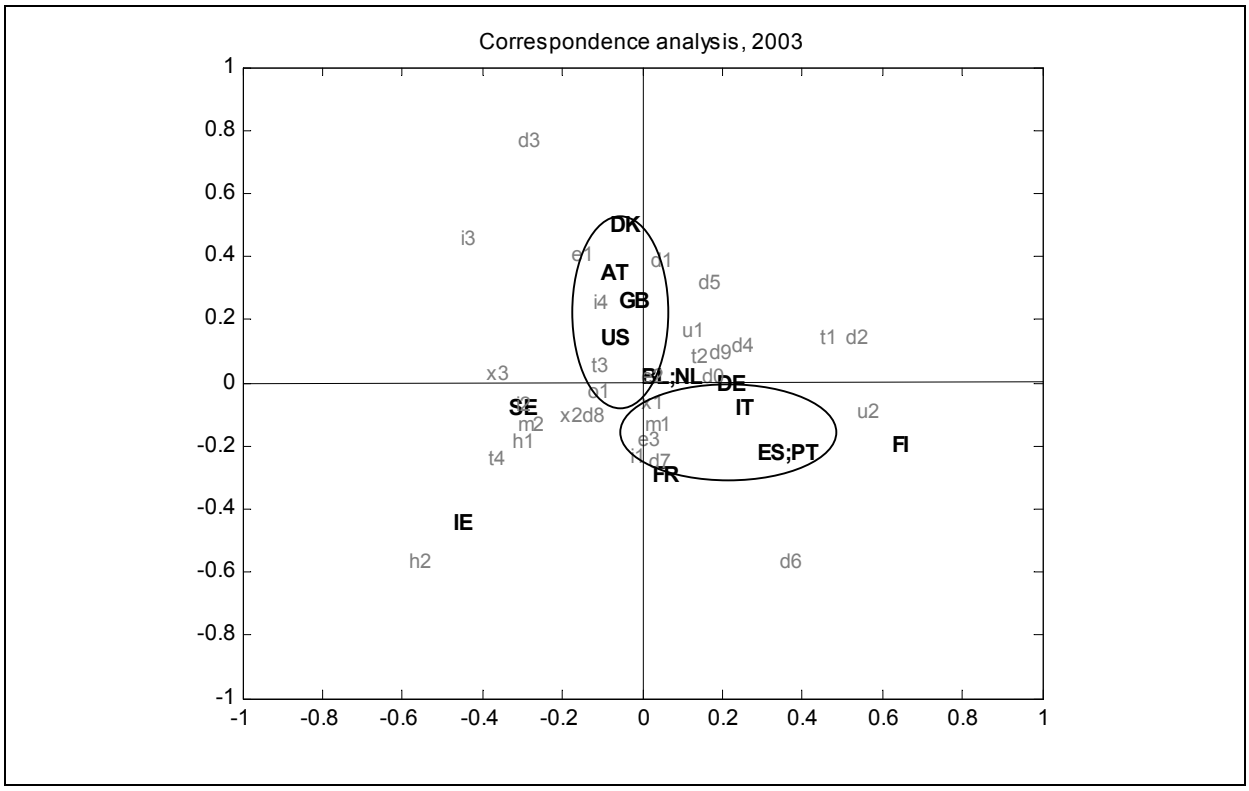
For comparing data points belonging to different groups one can interpret at the angle between a row point and a column point (taking the origin as the summit). If the angle between the points is acute (<90º) the two characteristics for which the points stand for are correlated. On the contrary, if the angle is obtuse, the points are negatively correlated. Finally, if there is a right angle, the points do not interact.

Figure 7. Correspondence analysis: countries' patterns of specialisation, 1996



Source: Eurostat (2004b).

Figure 8. Correspondence analysis: countries' patterns of specialisation, 2003



Source: Eurostat (2004b).

The analysis allows us to disentangle the similarities between countries and products in terms of "trade balance", and to understand the competitive position of the countries across the different sub-markets. The analysis has been performed using data from the years 1996 (Figure 7) and 2003 (Figure 8).

The similarities between countries and their specialisation profile have changed over time. This happened particularly in the case of Ireland, where its "trade balance" profile was similar to those for the US and Germany in 1996, while it is placed quite far from these countries in 2003.

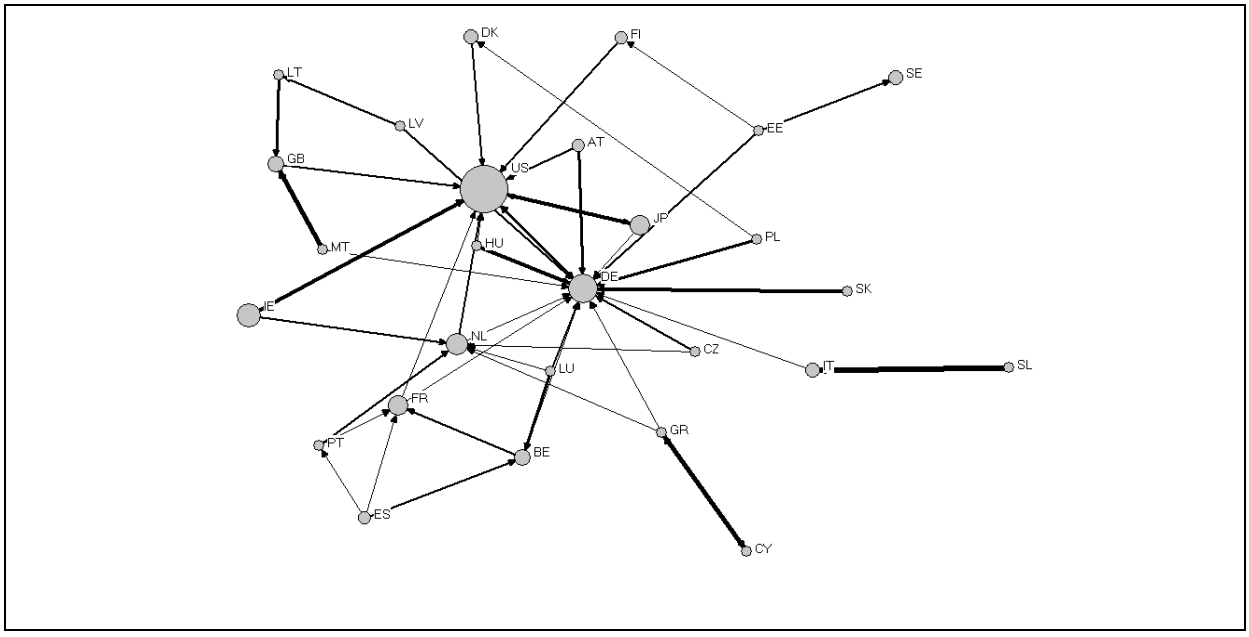
While in 1996 Germany and the US had very similar profiles (indeed the two countries are placed very close in the figure), in 2001 they have quite distinct profiles. In 2003, Germany, together with the Netherlands and Italy, has a profile that reflects specialisation in large diagnostic equipment (particularly ultraviolet and infrared apparatus, magnetic resonance imaging apparatus and apparatus based on the use of alpha, beta, or gamma radiation).

In both years, Finland has quite specific features, being specialised in MRI (d2) and X-ray apparatus for dental uses (d6). Spain and Denmark show similar profiles in both years.

Finally, in order to characterise the main partners of the EU countries and the US, we employed a network representation. Figure 9 visually represents the trade flows among the countries in the analysis.

The network has been built considering the share of exports for European countries, the US and Japan. The existence of a tie between country X and Y (i.e. of an arrow starting from X and pointing towards Y) means that the share of exports for the country X to the country Y is greater than 15% (where shares have been computed over the total value of exports to the countries included in the analysis). The size of each country (node) in the drawing is proportional to the value of the exports of the countries to the other countries included in the analysis.

Figure 9. Network representation of international trade flows, 2003



Source: our elaborations on Eurostat (2004b), US International Trade Commission (2004).

The picture clearly shows the role of the US as the preferred partner of European countries and Japan. Germany is the European country with the largest export value and also the one with the most number of ties with other countries. Japan has ties with the US and Germany. Ireland has significant commercial ties with the US and the Netherlands.

5.3 Market structure

In this section we will develop indicators of market structure and dynamics, and we will present the results both at the aggregate level (for the whole medical device industry) and at the level of specific medical device sub-sectors.

This section, more than the others, has been limited by poor data availability and quality.

a. Number and size of firms

A first account of the structure of the medical device industry can be obtained by the number of firms that are active in the countries taken into consideration. The US Census Bureau reports in the 2002 data for about 6,007 establishments[24] operating in the medical device sector. Another useful source is given by the FDA establishment registry[25]. The FDA register 11,409 US establishments involved in the manufacturing of medical devices owned by 10,027 corporations (about 2 percent are non-US owner groups).

For the European countries (EU-25), the NewCronos database (Eurostat, 2004a) reports about 50,000 enterprises[26] operating in the NACE 33.1. Eucomed (2004) reports about 8,500 companies in Europe, while the European establishments registered with the FDA are 1,887, owned by 1,793 different groups (11.27 percent are US companies).

A total of 5,040 companies are registered in Japan with the JFMDA, with 1,289 companies registered with the Japan Association of Health Industry Distributors. Japanese establishments registered with the FDA are 540 (457 owner groups).

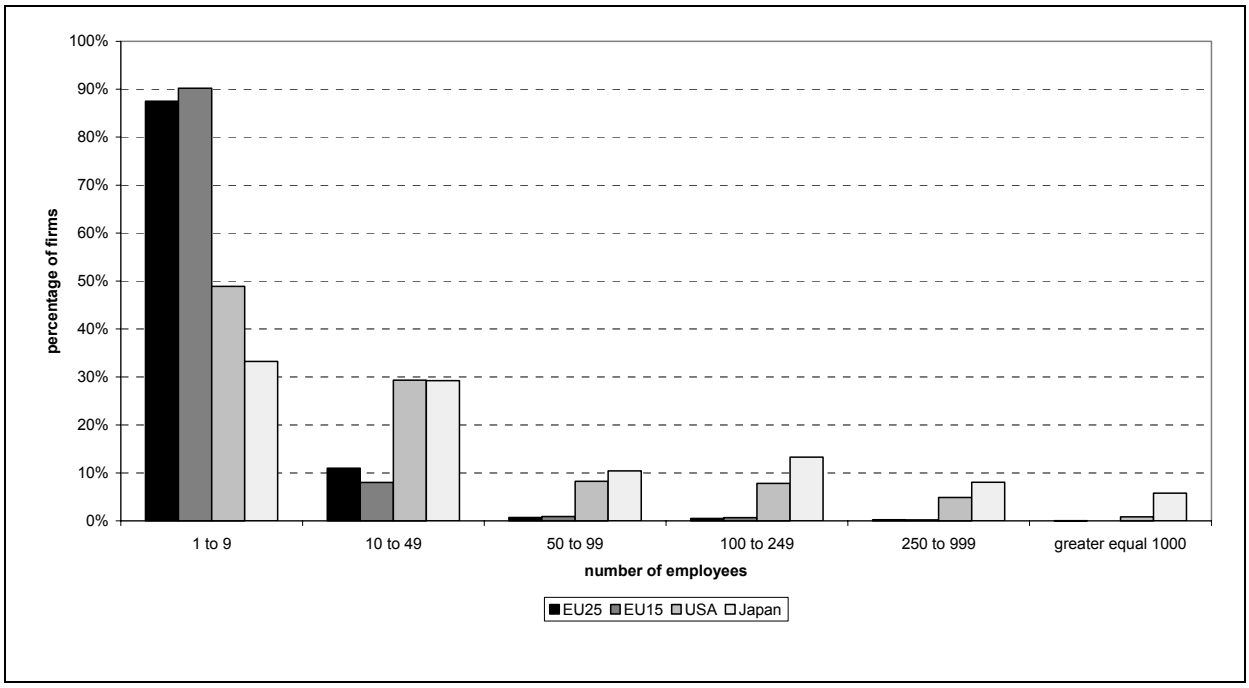
The composition, in terms of firm size, of the medical device industry in the US, the EU (both EU-15 and EU-25) and Japan is depicted in Figure 10, which reports the percentage of firms within classes defined according to the number of employees. The EU is characterised by a large share of small firms: more than 80 percent of the enterprises are small with less than 10 employees.

[24] "An establishment is a single physical location at which business is conducted and/or services are provided. It is not necessarily identical with a company or enterprise, which may consist of one establishment or more" (see http://www.census.gov/econ/census02/text/sector00/estab.htm).

[25] The registry lists all the "establishments engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of medical devices intended for human use and commercial distribution. Foreign establishments that export to the U.S are also required to register" (see http://www.fda.gov/cdrh/databases.html). Detailed information about the operation activities of each registered establishment and its owner group are reported. Also the country of the establishment and of the owner group is reported.

[26] An enterprise is defined as "the smallest combination of legal units which constitutes an organisational unit for the production of goods and services enjoying certain decision-making autonomy, in particular for the allocation of its current resources. An enterprise carries out one or more activities in one or more places. An enterprise may correspond to a single legal unit" (Eurostat, 2003).

Figure 10. Size distribution of the firm in the medical device industry, EU (2001), US and Japan (2002)



Source: Eurostat (2004a); US Census (2004); MHLW (2003).

As for Japan, data are based on a survey of about 2,800 medical device firms performed by the MHLW (MHLW, 2003). 1,574 companies participated in the survey, yielding a 56.2 percent response rate. It is likely that no response firms are very small due to the lack of personal resources. However, if non-respondent firms were all in the 1-9 employees category, the share of those firms over the total would be roughly 65 percent, still lower than the share of small firms in the EU.

Table 6 reports the distribution of the number of employees by firm size[27] and, in the last column of the table, an index that compares the average number of employees per establishment/enterprise in the medical device industry and the same figure in the total manufacturing industry[28]. The interpretation of the size index is the following: it represents the average size of the enterprises/establishment in the medical device industry as a percentage of the average size of the enterprise/establishment in the manufacturing industry.

[27] Analogously with Figure 10, firm size is measured in terms of the number of employees. The table differs from the graph since the share of the number of employees (rather than the share of the number of firms) is considered.

[28] The average size of the enterprise/establishment has been computed as the ratio of the total number of employees over the number of enterprises/establishments for each country. Then the size index has been obtained taking the ratio of the average size in the medical device industry and the average size in total manufacturing, multiplied by 100.

Table 6. Number of employees, by firm size (employees)

	Number of employees	1-19 (%)	20-49 (%)	50-99 (%)	100-249 (%)	250-499 (%)	500-999 (%)	more than 1000 (%)	Size index
US	361,384	5.78	7.87	9.61	20.48	18.13	18.32	19.81	142.41
EU15	308,019	41.22	12.98	7.25	11.84	4.73	2.47	0.00	52.00
NMS	409,67	37.16	8.08	6.55	7.87	1.89	9.86	0.03	10.66
EU25	358,500	39.94	12.75	8.23	12.52	8.37	8.90	n.a.	41.77
Germany	145,037	47.02	13.47	7.18	9.11	6.23	n.a.	n.a.	39.24
France	42,527	38.84	12.22	8.55	15.37	n.a.	4.91	n.a.	34.43
UK	35,082	30.41	13.43	9.29	22.04	n.a.	8.50	n.a.	89.20
Italy	25,692	43.45	15.89	8.50	16.05	6.25	9.86	0.00	20.22
Poland	17,229	49.94	4.35	8.56	9.23	4.49	23.44	0.00	28.54
Ireland	14,770	0.81	2.16	4.08	n.a.	n.a.	n.a.	n.a.	n.a.
Spain	11,845	54.46	19.19	n.a.	11.71	0.00	n.a.	0.00	25.85
Sweden	9,356	22.93	13.44	6.62	n.a.	28.89	n.a.	n.a.	56.44
Czech Rep.	8,649	35.69	14.29	12.79	8.02	n.a.	n.a.	0.14	57.30
Denmark	7,142	15.57	n.a.	7.62	21.06	17.08	n.a.	0.00	75.82
other	31,657	44.62	12.42	3.74	9.18	0.00	0.00	0.00	--

Source: US Census (2004); Eurostat (2004a).

The average size of the US establishment in the medical device industry is 142.41 percent the average size for the total manufacturing sector, pointing to a size of medical device establishments that are, on average, larger than the industry as a whole. The opposite is true for the European countries, where the average medical device enterprises are smaller than the average enterprise in the total manufacturing. Together with the size distribution depicted in figure 10, this result points to a different composition in terms of size of the firms operating in the medical device industry in the US with respect to the EU, where the industry is populated by small firms. This may have relevant implications in terms of available resources and funding of research activities. Another relevant aspect concerns the level of diversification both across sub-industries, and within each segment of the firms' production.

b. Corporate ownership

In order to characterise the medical device industry in terms of diversification of the actors involved, we employed FDA data. This data source allows an analysis at the sub-market level, since all products commercialised in the US are listed and classified according to their product class and medical specialty (see Table A.5.6 in Annex 5). The classification comprises 4,950 product classes, grouped into 19 medical specialties. In addition, for each product the database lists the establishment involved in the manufacturing activities and its owner group, providing a useful source of information for computing the share of ownership by home country corporations, European corporations (we considered EU-15 plus Switzerland and Norway), US and Japanese corporations, for each country (with at least one manufacturer registered with the FDA). Results are reported in Table 7.

The fact that the database refers to the US could determine a bias towards US corporations; however, given that the US is the largest market in the world, and that it is targeted by most world producers, the following analysis has a good level of generalisation, and can provide relevant information about the structure and the characteristics of the medical device industry.

Table 7. Share of corporate ownership, by establishment country

Establishment Country	Owner/Operator Group Country (%)					
	Europe	Home	Japan	Other	US	N
US	1.29	98.24	0.15	0.32	0.00	11,406
Germany	92.94	91.07	0.21	0.21	6.65	963
Canada	0.37	91.70	0.18	0.00	7.75	542
UK	86.76	83.88	0.38	0.38	12.48	521
Japan	0.60	97.82	0.00	0.00	1.59	504
Italy	96.67	93.79	0.00	0.67	2.66	451
France	88.54	84.72	0.35	1.04	10.07	288
Switzerland	98.02	83.82	0.00	0.58	10.40	173
Sweden	91.52	86.67	0.00	0.61	7.88	165
Netherlands	88.51	81.61	0.00	0.00	11.49	87
Denmark	91.77	90.59	0.00	1.18	7.06	85
Ireland	38.56	31.33	0.00	1.20	60.24	83
Spain	90.00	80.00	0.00	0.00	10.00	60
Belgium	91.49	87.23	4.26	0.00	4.26	47
Finland	82.61	78.26	0.00	0.00	17.39	46
Austria	95.55	84.44	0.00	2.22	2.22	45
Hungary	20.00	65.00	0.00	0.00	15.00	20
Norway	90.00	85.00	0.00	0.00	10.00	20
Poland	6.25	93.75	0.00	0.00	0.00	16
Czech Republic	7.69	84.62	0.00	0.00	7.69	13

Establishment Country	Owner/Operator Group Country (%)					
	Europe	Home	Japan	Other	US	N
Estonia	25.00	50.00	0.00	0.00	25.00	4
Luxembourg	100.00	100.00	0.00	0.00	0.00	4
Portugal	75.00	50.00	0.00	25.00	0.00	4
Slovakia	33.33	0.00	0.00	0.00	66.67	3
Ukraine	33.33	66.67	0.00	0.00	0.00	3
Lithuania	0.00	100.00	0.00	0.00	0.00	2
Malta	50.00	0.00	0.00	0.00	50.00	2
Greece	100.00	100.00	0.00	0.00	0.00	1
Slovenia	0.00	100.00	0.00	0.00	0.00	1

Source: our elaborations on FDA (2004c). Europe is EU-15 plus Switzerland and Norway.

European ownership of US establishments is not as strong as US ownership of European establishments. Indeed, while 1.29 percent of US establishments are owned by a European corporate group, US corporations own 6.65, 12.48 and 10.07 percent of respectively German, British and French establishments. The share is very large for Ireland: 60.24 percent of Irish establishments registered with the FDA are owned by a US corporation.

The US ownership is reduced for the Japanese establishments where only 1.59 percent of Japanese establishments is owned by the US. On the reverse side, only 0.15 percent of US establishments is owned by a Japanese corporate group.

The high ownership of European establishments by US corporations can be attributed to the large M&A activities that have involved US and European corporations during the 1990s (see the analysis in the next chapter).

c. Specialisation and diversification of national production

Using the information about the product commercialised by each establishment and the country of its corporate group, we have computed the level of specialisation of each country, as measured by a Herfindahl-type index of concentration and by the share of the top medical specialty.

The Herfindahl index of concentration is computed as $\sum_{j=1}^{19} s_{ij}^{\,2}$ where s_{ij} is the share of products commercialised by corporations from country i in the medical specialty j. The shares have been summed over the total number of medical specialties (19), and the index has been computed separately for each country.

Table 8 lists the total number of firms by nationality of the owner group, the share over the total and the Herfindahl and C1 indexes.

The C1 index is the share of the largest medical specialty in each country, providing information about the level of specialisation of country's activities. On average, European countries are more specialised than the US: the level of both the Herfindahl index and of the C1 index are higher. Also Japanese production is more specialised than the US production:

24.25 percent of the production by Japanese corporation is concentrated in one medical specialty.

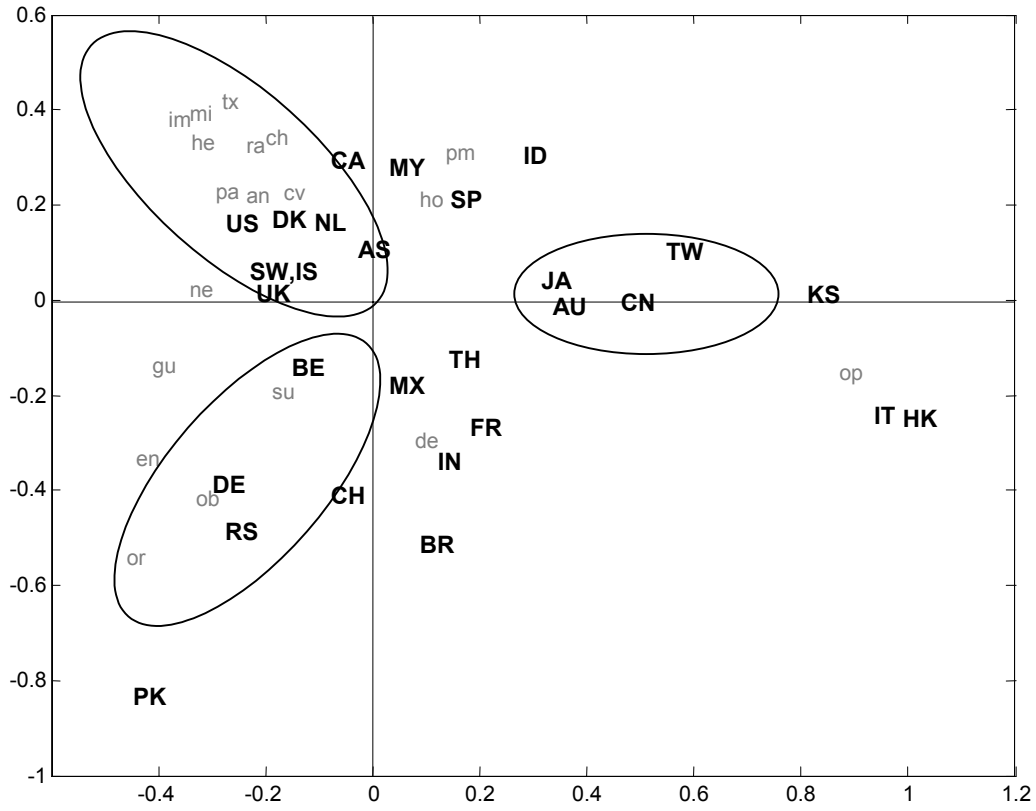
Table 8. Diversification of country products

	N	%	Herfindahl	C1
US	10,976	46.64	0.0748	13.11
Germany	1,756	7.46	0.0834	16.34
China	1,727	7.34	0.1532	21.89
Taiwan	1,205	5.12	0.1522	25.31
Pakistan	1,166	4.95	0.1347	23.84
South Korea	691	2.94	0.1926	35.75
Canada	683	2.90	0.1024	21.23
UK	657	2.79	0.0818	17.50
Italy	553	2.35	0.2580	47.92
Japan	544	2.31	0.1070	24.45
Hong Kong	518	2.20	0.2397	40.93
France	370	1.57	0.1057	22.97
India	295	1.25	0.1324	21.69
Israel	257	1.09	0.0840	14.01
Switzerland	218	0.93	0.1064	20.64
Sweden	215	0.91	0.0815	13.95
Malaysia	172	0.73	0.3949	60.47
Denmark	124	0.53	0.0748	12.90
Australia	118	0.50	0.0975	18.64
Mexico	104	0.44	0.1407	23.08
Netherlands	100	0.42	0.0904	16.00
Thailand	91	0.39	0.2424	40.66
Brazil	90	0.38	0.1398	25.56
Spain	79	0.34	0.1027	15.19
Belgium	65	0.28	0.0845	13.85
Russia	61	0.26	0.0922	13.11
Austria	52	0.22	0.1213	23.08
Indonesia	50	0.21	0.3032	52.00

Source: our elaborations on FDA (2004c). Europe is EU-15 plus Switzerland and Norway.

To dig further into the patterns of specialisation in countries, we have applied the correspondence analysis to the matrix containing the number of products in each medical specialty by nationality of the owner corporate group (see Figure 11 – only countries in Table 8 are considered).

Figure 11. Correspondence analysis, all countries



Specialty codes: an: anesthesiology; cv: cardiovascular; ch: clinical chemistry; tx: clinical toxicology; de: dental; en: ear, nose, throat; su: general and plastic surgery; ho: general hospital; gu: gastroenterology/urology; he: haematology; im: immunology; mi: microbiology; ne: neurology; ob: obstetrics-gynecology; op: ophthalmic; or: orthopedic; pa: pathology; pm: physical medicine; ra: radiology.

Source: our elaborations on FDA (2004c, 2004d).

Japan, China, Taiwan, and Austria show a similar specialisation profile. The northern European countries (Denmark, Sweden, and the Netherlands, and to some extent the UK) show a specialisation profile that is similar to that of the US, structured around anaesthesiology, cardiovascular, and pathology devices. Belgium and Germany show a different profile and are specialised in obstetrics-gynaecology, general and plastic surgery, and orthopaedic.

Due to the different classification systems employed, it is not possible to compare directly the trade data and the specialisation profile of the countries on the product side.

Finally, we analysed data at the manufacturer level and we consider an entropy-based measure of diversification (Berry, 1975). This index value is zero when the firm's products are concentrated within a single medical specialty. At the other extreme, if the firm's products are spread evenly across the *K* existing specialties, the firm's entropy reaches its maximum equal to log*K*. Since the classification in the FDA listing is a hierarchical method of classification, and each product can be framed within a larger group defined by a higher level of aggregation (i.e. the medical specialty), we decomposed the firm's total entropy into two components: the entropy that exists between and within product classes, providing respectively basic measures of 'broad-spectrum' and 'narrow-spectrum' diversification (Baldwin, Beckstead, Gellatly, and Peters, 2000). These measures are defined as follows.

Let G be the number of sub-classes within each medical specialty and S_g the share of firms' products within class g. We indicate with s_i the share of the sub-class i within class g.

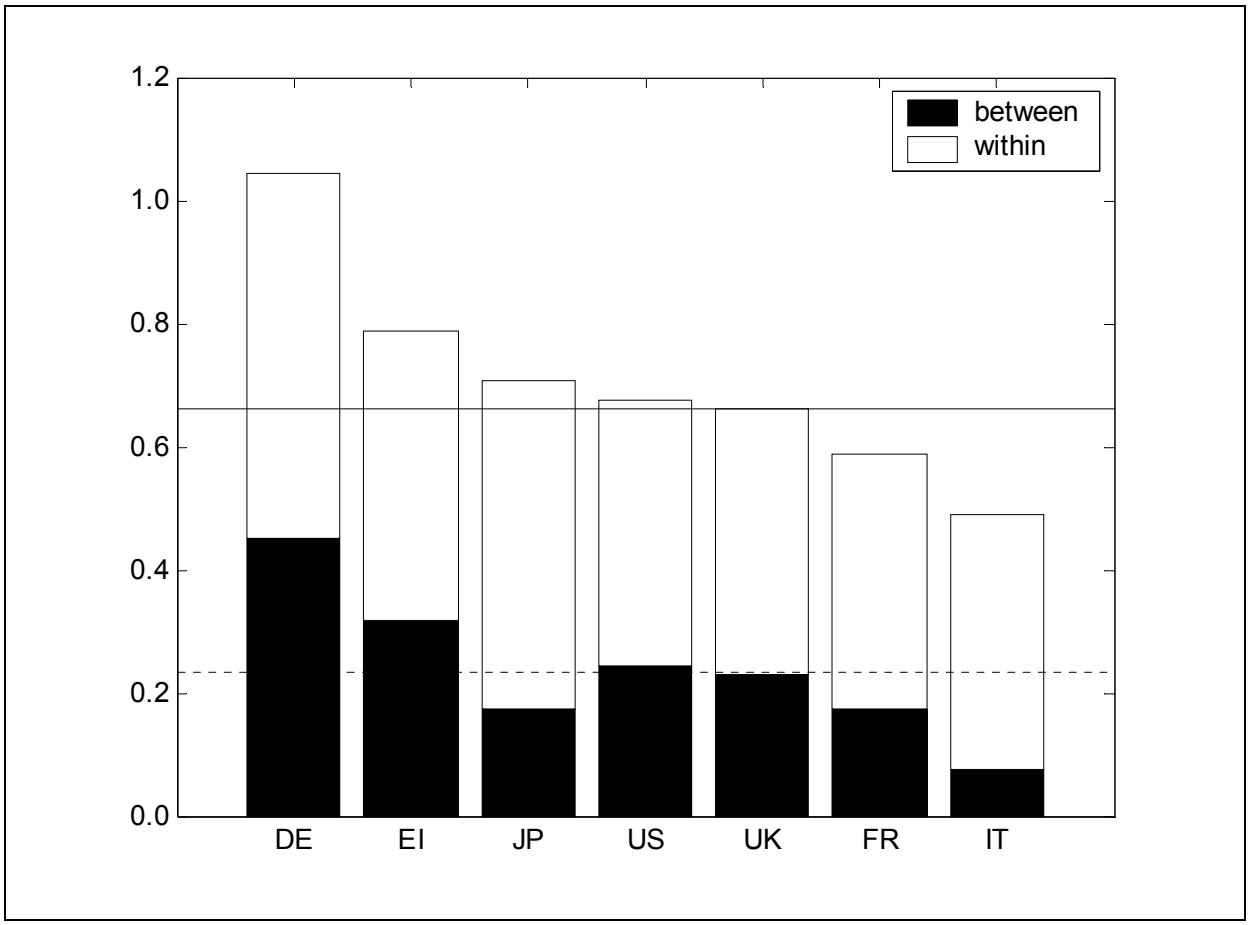
The entropy between groups is defined as: $\sum_{g=1}^{G} S_g \log(1/S_g)$, while the entropy within a group is: $\sum_{i \in S_g} (s_i / S_g) \log(S_g / s_i)$. Those indexes allow us to evaluate separately the effect of the distribution of firm products across separate medical specialties and the distribution of firm products among different sub-classes within a medical specialty.

Results are represented in Figure 12. The continuous and the dotted lines represent respectively the average index of total diversification and the average index of between-entropy diversification.

Germany is the country whose firms have a higher level of diversification and neither within nor between diversification plays a larger role in the level of diversification. Also Irish firms present a high degree of diversification, followed by Japan and the US. The Japanese firms have a diversification profile where the within diversification, i.e. the diversification of products within a medical specialty, plays a larger role (the index of between diversification account for about the 25 percent of the total).

Italy is the country with the lowest level of diversification (among the countries considered) and its level of diversification is driven by the diversification within medical specialties.

Figure 12. Average entropy diversification index (within and between), by country of corporation

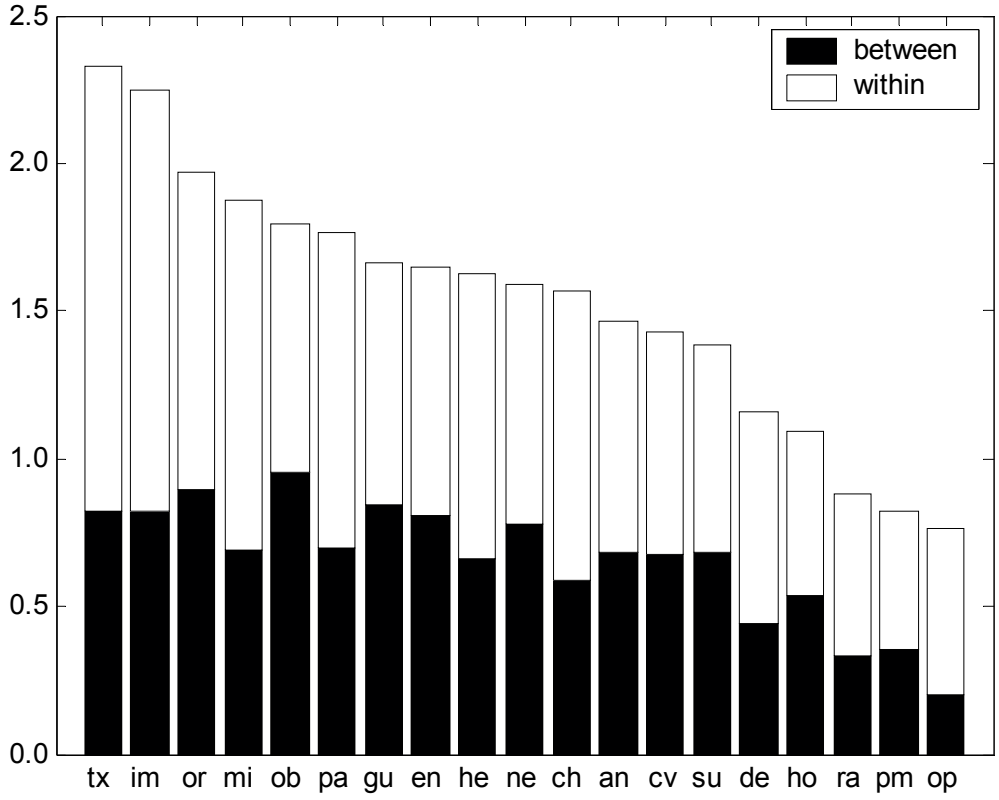


Source: our elaborations on FDA (2004c, 2004d).

On the other side, grouping the firms according to the medical specialty they are active in, quite different diversification profiles emerge across medical device sub-markets.

Firms operating in clinical toxicology and immunology show the larger level of diversification, whereas the larger role is played by a pattern of diversification into products belonging to the same medical specialty. The group with the highest relative contribution of the diversification across medical specialties (between-entropy) is given by obstetrics and gynaecology. This result confirms once again the high heterogeneity of the medical device industry, characterised by different sub-markets with different characteristics.

Figure 13 Entropy across medical specialties



Specialty codes: an: anaesthesiology; cv: cardiovascular; ch: clinical chemistry; tx: clinical toxicology; de: dental; en: ear, nose, throat; su: general and plastic surgery; ho: general hospital; gu: gastroenterology/urology; he: haematology; im: immunology; mi: microbiology; ne: neurology; ob: obstetrics-gynaecology; op: ophthalmic; or: orthopaedics; pa: pathology; pm: physical medicine; ra: radiology.

Source: our elaborations on FDA (2004c, 2004d).

6. R&D AND INNOVATION

Summary of the chapter

In this chapter we take into account different aspects of the innovation process in the medical device sector from patents and scientific publications to the introduction of new devices on the market. This analysis is performed in order to assess the level of innovativeness of the European medical device industry and to compare it with the ability to innovate of firms and institutions operating in the US and Japan.

First, in order to characterise the innovation process in medical devices, we present a set of indicators building upon patents and patent-based measures. The analysis of the information about the innovative activities contained in patents highlights the large role for small firms and individuals in the innovation process in this industry. Also the knowledge base of the medical device industry is more diversified in terms of technological classes, pointing to a higher level of interaction between areas in the sector. Here innovation is often related to the introduction of new materials or new technologies that have been developed outside the medical industry. This result is also confirmed by the diversification profiles of the firms innovating in the industry, being active on a more diverse portfolio of technological classes.

The analysis of the R&D intensity of the sector and the comparison with the US and Japanese industries and within Europe across industries, is limited by the inadequacy of the data available. The results point to a lower level of R&D intensity of the European firms compared to the US. However, this result needs to be treated with caution. High heterogeneity in terms of R&D intensity exists across European Member States, and France and Germany are the top R&D spenders, followed by UK and Italy. High heterogeneity exists within the industry: different sub-markets are characterised by different level of R&D intensity, where high-tech segments (in-vitro diagnostics on top of all) present the highest R&D intensity, while traditional low-tech segments (laboratory apparatus and furniture, surgical appliance and supplies) are associated to the lowest.

The analysis of the flow of R&D licensing agreements also reveals the role of the US firms as net exporter of technologies. Quite different patterns characterise the different segments, and the European countries appear to be net exporters of technologies related to implantable devices, and of therapeutic equipment and supplies, with respect to the US.

As for collaborative agreements and licensing agreements for the sector, US show strong world dominance both as originator and as developer of licensing agreements. The analysis of the output side of the innovation process (number and quality of patents and publications, introduction of new devices on the US market) confirms to the leading role of the US, both in terms of numbers and “importance”.

All in all, the analysis points to a lower level of innovativeness of the European industry as compared to the US industry. This result, coupled with the evidence presented in Chapter 5, presents a picture where the European industry is lagging behind the US industry along multiple dimensions taken as proxy for its level of competitiveness and innovativeness.

6.1 Introduction and methodology

The innovative activity of firms in the medical device industry has significantly contributed to enhance health conditions by helping patients to live longer and better-quality lives. A mail

survey was conducted in the US, where primary care physicians were asked to assess the relative importance of thirty medical innovations. (Fuchs and Fox, 2001). The ten surveyed medical innovations with the largest score and their country of origin are reported in Table 1.

Table 1. Most important medical innovations and their country of origin

Rank	Technology	Description	Country of Origin
1	Magnetic Resonance Imaging; Computed Tomography	Non-invasive methods to view internal anatomy	US; UK
2	Angiotensin converting enzyme inhibitors	Drugs for hypertension and heart failure (main indications)	US
3	Balloon angioplasty	Minimally invasive surgery to treat blocked arteries	Switzerland
4	Statins	Drugs lowering cholesterol synthesis	US, Japan
5	Mammography	Radiographic examination of the breast (diagnostic tool to detect breast cancer)	US
6	Coronary artery bypass graft surgery	Surgical therapy of ischaemic coronary artery disease	US
7	Proton pump inhibitors; H2-receptor antagonist	Drugs reducing acid production in the stomach	Sweden; UK
8	Selective serotonin re-uptake inhibitors	Antidepressant drugs	US
9	Cataract extraction and lens implant	Eye surgery	US, UK
10	Hip replacement; Knee replacement	Joint replacement with mechanical prosthesis	UK; UK, US

Source: Fuchs and Sox (2001), our search on the web.

Besides assessing the importance of medical technologies, the table suggests the leading role of the US in the innovation process. The United States is the country of origin of eight out of ten of the medical innovations considered. Among the European countries, the UK and Sweden are the only countries appearing in the list.

However, this is only part of the story. In this chapter, we attempt to characterise the innovation process in the medical device industry and to compare countries' competitive advantages and R&D intensity.

It is well known that measuring innovation is a difficult task and no single indicator can provide a satisfactory picture. We therefore take into consideration different aspects of the innovation process, looking both at the input and output sides of the research process, and different indicators are analysed to understand its characteristics.

The medical device industry is highly heterogeneous. Different sub-markets coexist that are characterised by products at different stages of the product life-cycle and that require a different level of resources and investments. Medical device products range from lattice balloons to large equipment for therapeutic and diagnostic purposes, requiring considerable investment and trained personnel for their functioning. Whenever data at the sub-market level

are available, the analysis will attempt to unravel those differences and describe the main characteristics of each sub-market. However, different data sources classify medical device products according to different criteria, making it difficult to compare country performances across different sub-markets and indicators. This has severely limited the extent and implications of our analysis.

In order to better understand the innovation process for the sector, we compared it with the pharmaceutical sector. It appears that many distinctive features characterise the nature of innovation in medical devices compared to innovation in pharmaceuticals. Using patent data from the NBER database[29], we highlight the main differences between the two industries, with respect to the cumulativeness of knowledge, originality and generality of the knowledge base, and to the typology of firms involved in the innovation process (Trajtenberg, Henderson, and Jaffe, 1997; Hall, Jaffe, and Trajtenberg, 2001a; Hall, Jaffe, and Trajtenberg, 2001b).

The first input to the innovative activity is given by the expenditure in R&D. The analysis of Eurostat data (Eurostat, 2004a), measured at a national level, allows us to shape the broad picture of the R&D activities performed in Member States. Then, we also consider data at the firm level to gather information about the R&D intensity of the firms operating in this industry and in specific sub-markets.

The analysis by firm size shows that smaller firms have a higher R&D intensity than the larger ones. This result suggests the existence of a division of innovative labour, where smaller firms are highly research intensive, while larger corporations have the resources and capabilities that are necessary for the development and commercialisation of new products. In order to shed light into this issue, we will analyse deals and collaboration agreements among medical device institutions, taking into consideration R&D collaboration and merger and acquisitions (M&A) as a means for appropriating knowledge originated outside the firm (and institution) boundaries. When compared to the pharmaceutical industry, mergers and acquisitions (M&A) have a higher incidence over the total number of deals.

However, R&D expenditure and collaborations only provide a limited perspective to the study of innovativeness. In particular, they convey no information about the output side of the innovation process. We further analyse corporations working in the medical device sector on the basis of scientific publications and patents. When looking at those measures of the innovative activity of organisations, we provide a detailed analysis of industry dynamics and firm level strategies, distinguishing on the basis of the location of the organisation under study. Given the nature of the products in the medical device industry, a close link with the clinical scene is critical for companies that are trying to innovate in the medical fields (see references in Roberts, 1987). The world of physicians and public researchers and the one of firms are characterised by a different set of incentives for the disclosure of their innovations (Dasgupta and David, 1984). Therefore taking into account both patents and publications, we aim at providing a more complete picture of the innovative effort in R&D.

The analysis of the number of patents published in the US[30] reveals the dominance of the US in terms of innovation capabilities. Using data on citations received by each patent (a high number of citations received by a given firm or country can be interpreted as a measure of the quality and relevance of its innovative activities), US dominance in the medical device sector

[29] See Hall, Jaffe, and Trajtenberg (2001b).

[30] Given the relevance of the US market, and the consequent fact that most innovations are also patented in the US, the picture from the patents in the US can provide relevant evidence on the general global patterns.

turns out to be even stronger than it appears from patent count data, also suggesting that, on average, patents assigned to US institutions have a relatively greater impact on future innovative activity. European countries and also Japan lag far behind, and overall those countries experience a decline in their relative position.

A similar pattern emerges from the analysis of scientific publications. When the nationality of the main author is considered, the top patenting countries are ranked high also in terms of the number of publications.

Finally, even though the analysis of the R&D side is important in gaining information about the most innovative countries in the medical device sector, the impact of new technology occurs at the diffusion stage, where clinicians play the most significant role (van Merode, Adang, Paulus, 2002). Even if a certain health technology is available in a country, its true impact can only be fully realised if there exists adequate dissemination of infrastructures in the healthcare industry. Among them, important factors determining diffusion are the availability of trained personnel and the attitude of the medical profession towards new technology, government pricing policies, technology assessment processes and the costs of common alternatives (see van Merode, Adang, Paulus, 2002).

As an example of the phenomenon of "under-utilisation" of advanced medical technology in Europe, consider the case of implantable cardioverter-defibrillators (ICDs), an established, safe, proven, and cost-effective treatment for ventricular tachyarrhythmias and reduction in sudden cardiac death rates. Notwithstanding their characteristics, only 8 percent of the clinically eligible patients actually receive an ICD[31]. Unfortunately, such detailed data are not available for the industry as a whole. As a more reliable measure of inventive output, we take into consideration the introduction of medical devices into the US market. Again, we do not dispose of data about sales of medical device products, therefore we are not able to assess their diffusion and to analyse the pattern in life cycle of medical device products.

6.2 The innovation process for medical devices

This section aims at characterising the key feature of the innovation process in the medical device industry. Innovation in the medical device industry can take many different forms ranging from new products (both new devices and modifications of old devices), to new manufacturing processes, and new modes of practice (Robert, 1987). We will employ both patent data, a useful source of information to describe the key features of the innovations, and data from studies published in the empirical literature in order to describe the main characteristics and patterns of the innovation process in medical devices.

The economic literature has long debated on the factors and incentives driving the rate and direction of the research effort undertaken by firms and institutions. The debate in the theoretical literature has focused the attention on "technology push" versus "demand pull" theories, the former considering the exogenous effect of science on technological change, while the latter regarding market growth and size as unique determinants of the decision to invest in R&D. Both theories only present a partial piece of the story. The decision to invest in R&D, and therefore the rate and direction of technological progress, is the result of the interplay between the advances spanning from basic science, institutional variables, and economic factors, namely market growth and size (Dosi, 1982, 1988).

[31] Source: Guidant estimates.

Scientific opportunity, assessment of the market potential and of the resources needed for development, and medical needs have been identified in the pharmaceutical research as the major drivers of the pharmaceutical decisions to invest in R&D (Crogham and Pittman, 2004).

In the case of medical device innovation, the market for new devices is not always well defined. Consider the story of cardiac pacemakers (see Kahn, 1991). A market survey, at the time of their first introduction, estimated a total of 1,000 patients around the world needing the device, a tiny market of no interest to major corporations. Once developed and introduced (by a small companies – at that time), the market turned out to be 200,000 units a year. An evaluation of a device before its diffusion into clinical practice can grossly undervalue the technology to a degree that only a small company would find the prospects interesting. Medical imaging, where devices are costly and complex, is the exception to this "small-company" rule (Kahn, 1991).

Also, in the medical device industry, product development is inherently linked to product usage; therefore, users play a significant role in shaping the rate and direction of the innovative activities (Shaw, 1985). Many technologies need further improvements when first adopted, and feedback from clinical practice are important to disclose shortcomings and potentials that could not have been revealed in earlier, pre-market evaluations (The Lewin Group, 1999). Also, physicians are a source of ideas for alternative uses of existing technologies. For example, beyond their original uses in ophthalmology and dermatology, lasers are used in gynaecology, gastroenterology, oncology, thoracic surgery, and other specialties. Thus, widespread use of a product in one field can cause physicians to innovate and seek applications in other fields (The Lewin Group, 1999).

In a pioneer study about the innovation process in the scientific instruments sector, Von Hippel (1975) found that 80 to 100 percent of the key innovations in technological categories related to scientific instruments were in fact invented, prototyped and first field-tested by users rather than by product manufacturers (see Table 2). The producers' role in such cases was restricted to product engineering (work to improve prototype reliability, manufacturability and convenience of use, while leaving its principles of operation intact), manufacturing, marketing and selling. The user was also involved in the diffusion of detailed information, on the value of the innovation and how the prototype may be replicated, to other users, colleagues and scientific instrument companies alike.

Table 2. User domination of instrument innovations

Category of Instruments	% user	# user	# mfg.
Gas chromatography	82	9	2
Nuclear Magnetic Resonance	79	11	3
Ultraviolet spectrophotometry	100	4	0
Transmission electron microscope	79	11	3

Source: von Hippel (1976).

This finding has been also confirmed by Shaw (1985), who proved that 18 out of 34 analysed innovations in the British medical equipment industry have been based on user prototype (see

also Roberts, 1987). In addition, he found that in his sample of 34 new products, 26 (76 percent) had been developed through multiple and continuous interaction between the user and the manufacturer, resulting in 22 new devices successfully introduced on the market (see Conway, 1993 for a review).

An alternative source of ideas is given by the academics, whether at universities or clinical settings. However, due to the different set of incentives at work in the "open science" (see Dasgupta and David, 1994), academics may be very productive in having ideas, but they only infrequently try to exploit them, regardless of potential personal and social gains. A closer interaction between the university and the industry would be beneficial to both worlds: on the one side, closeness to the clinical scene is beneficial for medical device innovation; on the other side, the industry is more apt at recognising potentially profitable ideas.

A critical contribution to medical device innovation is given by small firms[32]. Much of the medical device industry comprises small entrepreneurial companies that have significant roles in medical devices and diagnostics innovation (see also the findings in Section 6). Start-up firms have been disproportionately responsible for the innovation and early development of truly novel devices, including angioplasty catheters, artificial joints, cardiac support devices, diagnostic ultrasound, diagnostic test kits, and vascular grafts. In contrast, larger firms are more likely to pursue next-generation or incremental improvements, for example, by refining or building on current product lines for familiar markets (The Lewin Group, 1999).

In order to highlight this characteristic and compare the patterns in the pharmaceutical and biotechnology industry, we considered the size distribution of the firms and institutions involved in the innovation process, where we measured size in terms of the number of patents.

[32] Although small companies may be responsible for early innovation, many will ultimately collaborate with larger partners to bring their products to market. Large corporations in this field are primarily acquirers of new technology emerging outside their organisational boundaries (often through the acquisition of young companies), and are effective in enhancing and commercialising existing technologies (Roberts, 1987; The Lewin Group, 1999).

Box 1: Patents as a measure of innovative activities

Patents have been extensively used in the empirical literature as a proxy for the output of innovative activities (see Griliches, 1984, 1990). They represent a unique source of information for studying innovation, since they provide detailed information about the (patented) inventions. In particular, each patent reports the technological area of the innovation, the name of the inventor(s) and of the institution(s) owing the patent right and their location. Also, the patent contains reference to previous patents and to the scientific literature, identifying the previous research upon which the patent builds.

The main drawback of relying on patents as a means for measuring innovation is in the fact that not all inventions are patented. New inventions have to meet patentability criteria, i.e. the invention must be *novel*, *non trivial*, and with *potential commercial application*. Moreover, the propensity to patent varies over time and by technological field, making it difficult to compare patent counts across industries and over time. In addition, the firm owing the invention may strategically decide not to apply for a patent, preferring other means for protecting the intellectual property rights. For example trade secrets and lead times are considered to be effective in many industries.

Surveys have been conducted to validate the use of patents as proxy for innovations (see Cohen, Nelson, Walsh, 2000; Arundel and Kabla, 1998). All the studies have highlighted the existence of a marked difference among technological sectors. Among the others, Cohen, Nelson, Walsh (2000) investigate the "*medical equipment*" industry and highlight the importance of patents in this sector as a mean for appropriating returns from product and process innovation[33].

Driven by a different research question, the NBER/Case Western Reserve Survey of Patentees provided evidence of the validity of citations as a measure of the knowledge spillovers (see Jaffe, Trajtenberg, and Fogarty, 2000). Grounded in the view of technological change as a cumulative process, whereby each innovation build on the body of knowledge that preceded it and forms in turn the foundation for subsequent advances, citations in patents can be considered a good proxy for the evidence of a link between an innovation and its technological "antecedents" and "descendants", therefore providing useful information for characterising the innovation process (Trajtenberg, Henderson, and Jaffe, 1997).

The patent data employed in this section are extracted from the NBER database[34] (Hall, Jaffe, Trajtenberg, 2001b), reporting data about the US patents granted between 1963 and 1999. For patents granted in the period 1975-1999, the database also reports information about the patents cited in each patent document and a series of indicators, computed on the basis of citations that describe the key characteristics of the innovation. We considered the patents classified within the "Drugs and Medical" category, further classified into Drugs, Biotechnology, Surgical and Medical Instruments (S&MI) and miscellaneous.

We considered all assignees active in the categories considered, and counted their total number of patents. Then we measured the number of assignees with a given number of

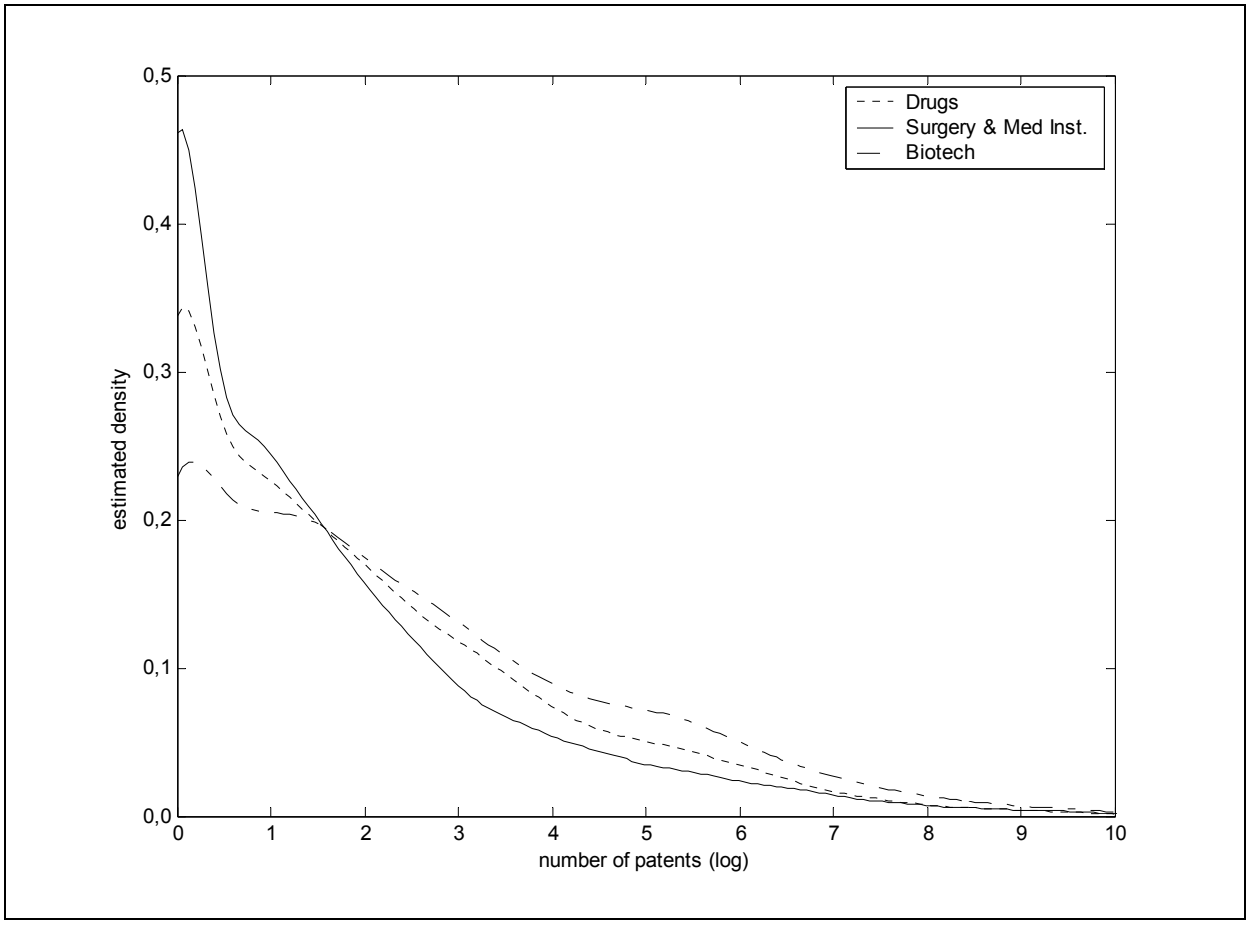
[33] Cohen, Nelson, Walsh (2000) report the results from a survey aimed at assessing the nature and the strength of appropriability conditions. The survey, the Carnegie Mellon Survey, was conducted in 1994 on more than 1000 R&D laboratories in the US manufacturing sector. The "medical equipment" industry turns out to be the one where patents are considered most effective as a mechanism for appropriating returns from product innovation (the mean percentage of product innovation for which patents are considered effective is 54,70 against 50,20 in the drug industry). Also lead time is considered an effective appropriation mechanism (effective in 58,06 percent of product innovations). For process innovations, the score is reduced, but it is still one of the highest across industries. Secrecy and complementary manufacturing in this case turn out to be most effective (see Cohen, Nelson, Walsh, 2000, Table 1 and Table 2).

[34] The NBER database contains information about all US patents granted between January 1963 and December 1999 and information about citations for patents granted in the period 1975-1999. Trends and country profiles will be analysed using ATAdb since this contains data up to the year 2003.

patents and used a Kernel technique to estimate the density function of the size distribution in terms of the number of patents[35].

Results are presented in Figure 1.

Figure 1. Size distribution (log of the number of US patents) in Drugs & Medical



Source: NBER patent database.

The S&MI category is populated by a large fraction of firms with a low number of patents. Indeed the share of assignees with only one patent is 35% in S&MI, while it is 28% in Drugs and 21% for biotechnology (see also the findings in Section 6).

When comparing the distributions (using a Kolmogorov-Smirnov test), the size distribution in the S&MI is different from the distributions that characterise the pharmaceutical and biotechnology industries. Firms in the pharmaceutical and biotechnology industries are, on average, larger than those active in the S&MI sector.

In addition, supporting a role for the user in the medical device innovation process, the share of patents assigned to individuals in this industry is larger than 2 percent, against 1,1 percent for the total database (see Hall, Jaffe, Trajtenberg, 2001b) and compared to 0.75 and 0.65 percent respectively for Drugs and Biotechnology patents.

[35] In order to enhance the graph's readability, the logarithm of the number of patents has been considered.

Inter-relation in different areas is another key feature of the medical device industry. Many fields of science, including materials science, bio-engineering, molecular biology, computer sciences, management, and telecommunications significantly contribute to the medical device innovation process. Many healthcare technologies are adaptations from other fields, for example, lasers, ultrasound, magnetic resonance spectroscopy, and computing. Among the many technologies that were developed through the interdisciplinary work of clinicians and physicists, engineers, and other scientists are medical lasers, cardiac pacemakers and defibrillators, cochlear implants, endoscopies, catheters, and cardiac imaging (The Lewin Group, 1999).

Citations in patents can be used to compute measures that capture different features of the (patented) innovation, and their links to other innovations. The NBER database reported the measures of *generality* and *originality* as defined in Trajtenberg, Jaffe and Henderson (1997).

The measure of originality for a patent i is a Herfindahl type index of specialisation computed as:

$$1 - \sum_{j=1}^{n_i} \left(s_{ij}\right)^2 ,$$

where s_{ij} denotes the percentage of citations made by patent i to patents belonging to the patent class j, out of n_i patent classes. Thus, if a patent cites previous patents belonging to a wide range of fields, the measure will be high, whereas if most citations are concentrated in a few fields it will be close to zero. Therefore, patents with a high value of originality are influenced by patents in different fields, pointing to inte-rrelation between areas of research, since it builds upon innovation in a variety of fields.

The measure of generality is built in an analogous way, but it is computed using citations received by subsequent patents. Building on the presumption (widely accepted in the empirical literature in the economics of technical change) that subsequent citations are indicative of the impact of a patent, a high generality score suggests that the patent had a widespread impact.

Table 3 reports the average values of the generality and originality indices for the categories we considered, and the average over the whole population of patents as a benchmark.

Table 3. Index of Generality and Originality, Drugs and Medical

Sub-category	Generality	Originality
Drugs	0.265	0.326
Biotechnology	0.271	0.274
Surgery & Med Inst.	0.324	0.366
Miscellaneous	0.252	0.266
Overall	0.321	0.349

Source: NBER patent database.

Compared with Drugs and Biotechnology, the S&MI category is characterised by a higher value of both the index of originality and generality. In particular, the value of the originality index suggests that patents in S&MI builds upon many different pieces of knowledge.

Another important information from patent citations spans from the assignee of the cited patents[36]. Citations are informative of knowledge spillovers (Jaffe, Trajtenberg, and Fogarty, 2000). Presumably, citations to patents that belong to the same assignee represent transfers of knowledge that are mostly internalised, whereas citations to patents of "others" are closer to the pure notion of (diffused) spillovers.

The NBER database provides a lower and an upper bound for the share of self-citations computed on the basis of the citation made by each patent. To have a more reliable measure we only included patents granted from 1990 to 1999.

The lower and upper bounds of the share of self-citations for the patents in the "Drugs and Medical" industry are reported in Table 4. Moreover, the average value computed over the whole sample (still for patents granted in the period 1990-1999) is also reported as a benchmark. Marked differences emerge between the drug and biotechnology industry and the medical device industry, as described by the S&MI category.

Table 4. Self-citations (%), Drugs and Medical

	Lower bound	Upper bound
Drugs	18.44	19.65
Biotechnology	14.08	14.66
Surgery & Med Inst.	7.42	9.47
Miscellaneous	7.01	9.42
Overall	11.68	13.22

Source: NBER patent database.

The difference in the share of self-citations between the various industries may well be the result of the size distribution of the firms. The pharmaceutical industry is indeed characterised by the presence of very large firms, and hence the likelihood that they will cite internally is higher. On the other side the S&MI category is populated by a large fraction of firms with a low number of patents (see Figure 1).

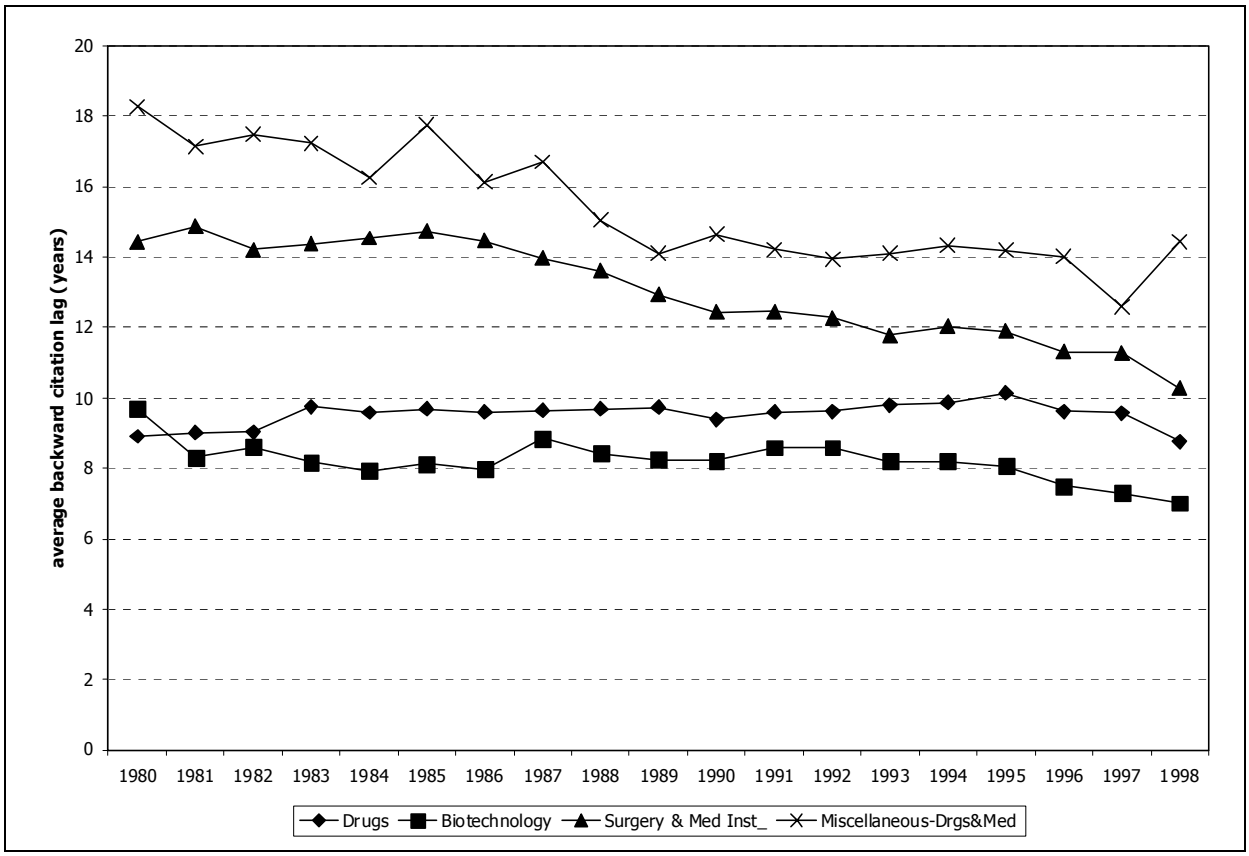
This pattern has nonetheless implications for the cumulativeness of knowledge within the industry. Self-citations might be the result of the cumulative nature of innovation and the increasing returns property of knowledge accumulation. In particular, this happens within a narrow field or technology trajectory, suggesting that the firm has a strong competitive position in that particular technology and is able to capture some of the knowledge spillovers created by its previous research (Hall, Jaffe, Trajtenberg, 2001a). The analysis highlights the low cumulativeness of knowledge in the medical device industry with respect to the innovation process in pharmaceuticals and biotechnology.

[36] Alternatively assignees in patents that subsequently cite the patent under analysis could be considered. However, since forward citations are affected from truncation, backward citations (i.e. citations made by the patent) are preferred since it is possible to get information over the whole distribution.

Under a complementary perspective, we take into consideration the backward citation lag, i.e. the time difference between the grant year of the citing patent and that of the cited patents. We preferred to use the backward citation lag rather than the forward citation lag. In fact, for patents granted from 1975, the NBER database reports the backward citation lag obtained from the complete list of citations made, while when looking at the time difference between the cited patent and the citation it receives (and therefore at forward citation lag), data are truncated since for more recent patents only a share of subsequent patents citing the patent under observation are observed.

The average backward citation lag is shortening for more recent patents in S&MI and for the miscellaneous category, while it remains rather constant for Biotechnology and Drug patents. On the technological side[37], the technology cycle in the S&MI is longer than Drugs and Biotechnology. In 1980, S&MI patents cited patents that were on average 14 years older, and this time lag has significantly shortened in recent years being 10 years for S&MI patents applied in 1998[38] (see Figure 2). This might be also the result of the higher inter-relation with other areas of the research in S&MI: more time may be needed to become aware of new material and improvements on the engineering side, and to introduce the innovations from other fields into medical technologies.

Figure 2. Average backward citation lag (years), Drugs & Medical



Source: NBER patent database.

[37] This must not be confused with the product life cycle, that we are not able to analyse given the lack of detailed data about sales of medical devices.

[38] Data for 1999 are not reported due to truncation in the patent series.

Finally, in order to characterise the activities of the firms involved in this industry, on a technological side, we considered all the patents assigned to non-government organisations with at least one patent classified into "Drugs and Medical", and we computed the entropy index of diversification (see Baldwin et al, 2000; and the description of the index in Section 5.3).

Firms operating in the S&MI subcategory have on average a lower overall diversification index (see Table 5).

Table 5. Entropy index of technological diversification

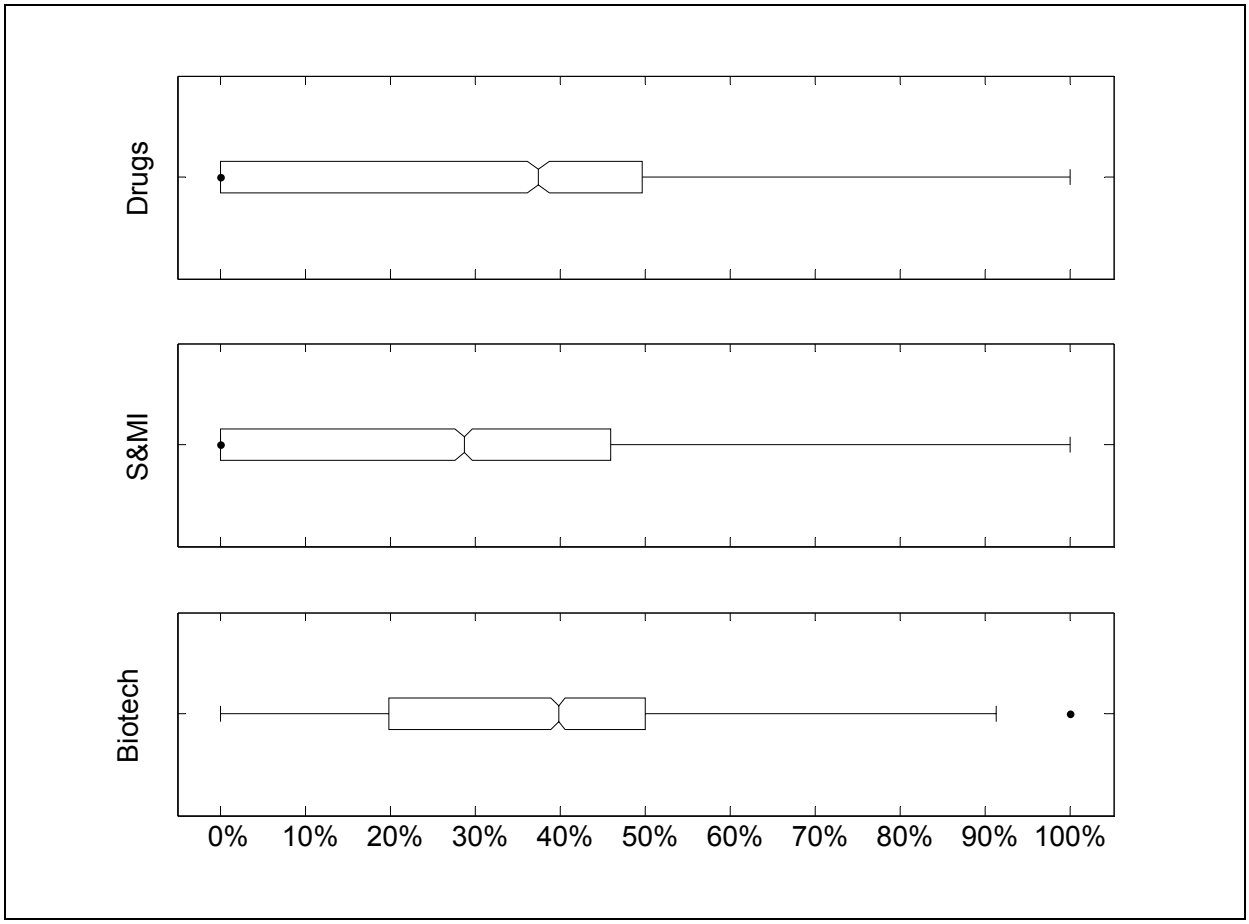
	Average	Median
Drugs	0.72	0.64
S&MI	0.60	0.00
Biotechnology	0.94	0.90

Source: NBER patent database.

An interesting feature of this index is the possibility to decompose the firms' total entropy (diversification) into two components: the entropy that exists between industry groups, and the entropy that exists within industry groups. We therefore computed both the within and between entropy and considered their respective contribution to the total entropy.

Figure 3 reports the boxplots of the share of the within entropy index over the total index of diversification for all the firms active in the Drugs, S&MI, and Biotechnology technological categories. The median of the shares of within entropy diversification is lower for the firms operating in the S&MI category with respect to Drugs and particularly with respect to Biotechnology. This means that firms operating in the S&MI have a higher incidence of between groups (or "broad-spectrum") diversification as compared to firms that are active in the Drug and Biotechnology sectors.

Figure 3. Share of Within Entropy over total diversification



Source: NBER patent database.

6.3 R&D intensity of the medical device industry

We start exploring the issue of R&D intensity of the medical device industry by comparing the share of R&D expenditure over turnover[39] in the medical device industry and selected sectors within European boundaries. Figure 4 reports the share of intra-mural R&D expenditure over turnover for the following NACE in the years 1999 and 2001.

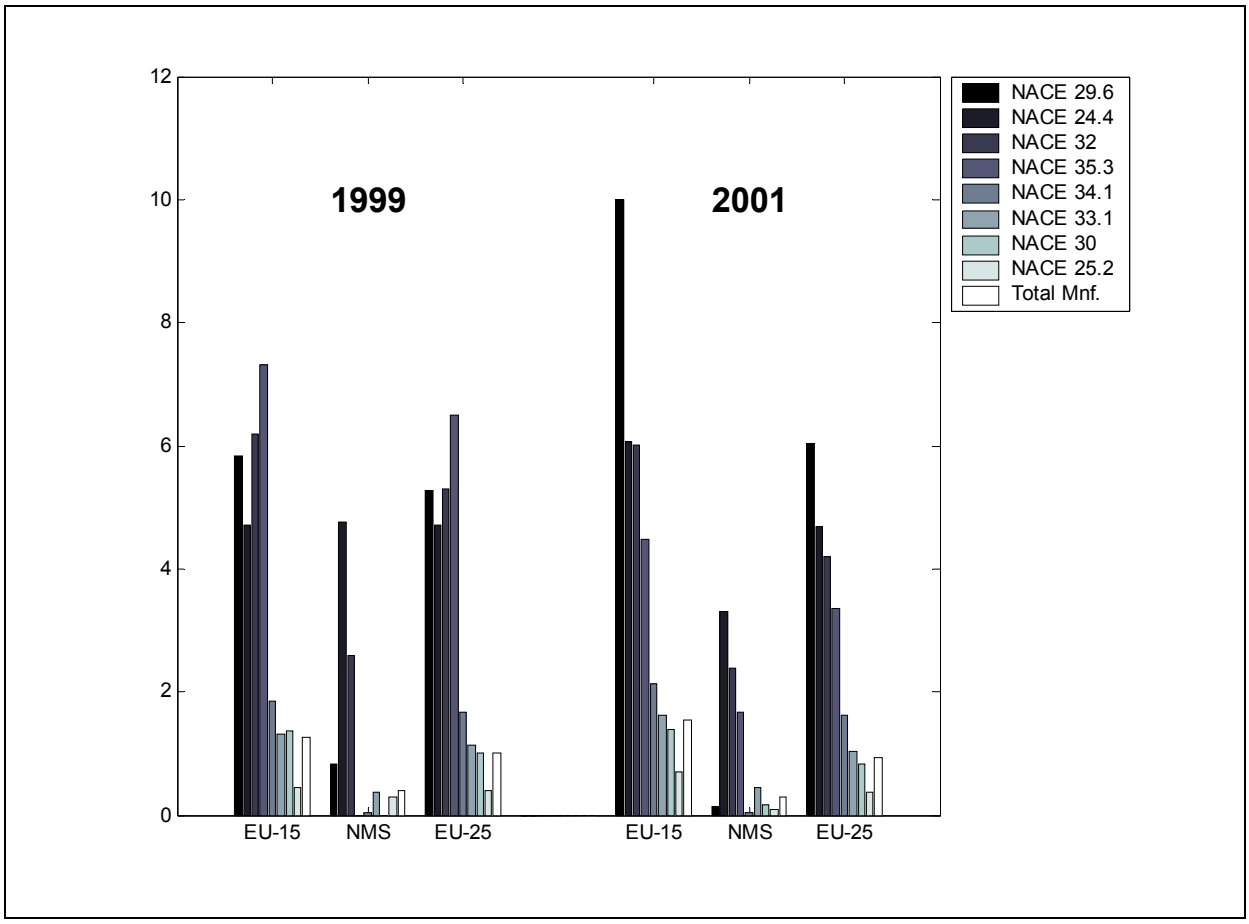
- NACE 29.6: Manufacture of weapons and ammunition;
- NACE 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products;
- NACE 32: Manufacture of radio, television and communication equipment and apparatus;
- NACE 35.3: Manufacture of aircraft and spacecraft;
- NACE 34.1: Manufacture of motor vehicles;
- NACE 33.1: Manufacture of medical and surgical equipment and orthopaedic appliances;
- NACE 30: Manufacture of office machinery and computers;

[39] Turnover is defined as the value of everything that is sold by the unit during the reference year, including goods sold from stocks and goods bought for resale (Eurostat, 2003).

- NACE 25.2: Manufacture of plastic products;
- NACE D: Total Manufacturing;

Data for the European countries are drawn from Eurostat, reporting information about the "Manufacture of medical and surgical equipment and orthopaedic appliances" sector (Eurostat, 2004a).

Figure 4: R&D over turnover for selected economic activities (NACE), 1999, 2001



Source: our elaborations on Eurostat (2004a).

The R&D intensity of the medical device industry is much lower than the R&D intensity of the pharmaceutical industry (NACE 24.4) and it has a similar level to that of the manufacture of motor vehicles (NACE 34.1) and office machinery and computers (NACE 30). Moreover, the R&D intensity of the sector has not changed substantially from 1999 to 2001 (see Table A.6.1 for details about data availability across the European countries).

Here we need to mention the inadequacy of the NACE classification for identifying the whole medical sector. In particular, Eurostat data only take into consideration the low-tech sub-markets of the sector, not including, among others, high-tech chemicals and biochemical-based devices such as in vitro diagnostics. As a result, the R&D intensity of the sector is highly under-estimated. Indeed, the ranking of the industries in terms of R&D efforts does not

match with a similar ranking published by AdvaMed (2004). AdvaMed considered the share of R&D expenditure over sales of the companies listed in the Compustat North America database published by Standard and Poor's. There the medical device industry ranked second in terms of R&D over sales, second only to the Drugs and Medicine industry.
The comparison of these figures is not straightforward and also the availability of different measures limits the comparison of the R&D effort of the European countries with the US and Japan. For the US and Japan we have data about the share of R&D over sales, while time series spanning a few years report data on turnover for the European countries. In addition, as we have already pointed out, R&D data for the European countries are biased downward making it difficult to compare the R&D intensity in Europe with that of the US and Japan. Despite these limitations, the data reported in Table 6 can provide useful insights. Even though using these data it is not possible to compare US dynamics to the pattern in Europe, we can observe within-country variations in the R&D intensity of the medical device sector. The ratio of R&D over sales has increased in the US from 8.4 percent in 1995 to 11.4 percent in 2002, a figure which is more than double that of Japan, reporting a share of R&D over sales that equals 5.6 percent.
On the other side, a different dynamic characterises the ratio of R&D over production, which is rather constant for the European countries.

Table 6. R&D as a percentage of turnover/sales, European Countries, the US, and Japan

Country	1995	1996	1997	1998	1999	2000	2001	2002
US	8.4	9.6	11.1	12.9	10.1	10.9	12.3	11.4
Japan	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	5.6
EU15	n.a.	n.a.	1.6	1.1	1.3	1.5	1.6	1.7
NMS	n.a.	n.a.	0.5	0.6	0.4	0.5	0.5	0.5
EU25	n.a.	n.a.	1.3	0.9	1.1	1.1	1.0	0.9

Source: AdvaMed (2004) for the US (data refer to publicly traded companies); Eurostat (2004a); MLHW (2003). See Table A.6.1 for details about the availability of EU Member States data.

In order to compare the R&D intensity in Europe, the US and Japan, Table 7 reports data drawn from Eucomed publications reporting the level of R&D expenditure as a share of sales in various years ranging from 1999 to 2003 (see Eucomed, 2004 for details).

Table 7. R&D expenditure as a % of sales, various years

	R&D/Sales (%)	Year
United States	12.90	1999
Japan	5.80	2000
EU average	6.35	--
Denmark	6.00	2002
France	3.00-5.00	2002
Germany	10.00	2003

	R&D/Sales (%)	Year
Ireland	1.52	2003
Portugal	0.05	2001
Spain	5.00-10.00	2002
Sweden	9.00	2001
United Kingdom	5.00	2000
Norway	0.00-8.00	2002
Switzerland	10.00-15.00	2002
Hungary	3.00-4.00	2001
Poland (figures based on NACE 33)	0.90	2002
Slovakia	0.50	2001

Source: Eucomed (2004).

The picture that emerges from the data reported in Table 7 is one where the R&D intensity of European firms is on average lower than that in the US, and slightly higher than the figure in Japan. High heterogeneity exists within European boundaries and the R&D intensity of Germany, Sweden and Switzerland is roughly equal to the ratio in the US.
Also the level of intra-mural R&D expenditures is highly heterogeneous (see Table A.6.1).

France and Germany are the top R&D spenders in Europe, followed by the UK and Italy. Different trends characterise these countries: France, Germany, and especially the UK are experiencing significant increases in the level of R&D expenditures in the medical device sector, while Italy presents a downward trend. The other European countries included in the analysis register a low level of R&D expenditures.

Next we analyse the R&D intensity for selected sub-markets. As already pointed out, the medical device industry is highly heterogeneous and characterised by sub-markets at different stages in the product life cycle, and requiring a different amount of resources.

The Compustat North America database (Standard & Poor's Compustat®, 2004b) reports information about R&D, sales, and the number of employees for the American and Canadian public companies. In addition, firms are classified according to the North America Industry Classification System (NAICS) and are assigned a code on the basis of the principal line of activity[40].

We considered the eight sectors reported in Table 8.

[40] R&D expenditure related to MD technologies by companies whose main line of activity is not classified in one of the NAICS included in the analysis is not considered. Also the R&D activity in sectors other than MD by large multinational companies with a main line of activity in one of the NAICS included are considered in the analysis. This is particularly relevant in the case of MD, where companies are characterised by "broad spectrum", i.e. across sectors, diversification (see the results in the previous Section).

Table 8. Sub-markets considered in the analysis

NAICS	Description
325413	In-Vitro Diagnostic Substance Manufacturing
339111	Laboratory Apparatus and Furniture Manufacturing (pt)
339112	Surgical and Medical Instrument Manufacturing (pt)
339113	Surgical Appliance and Supplies Manufacturing
339114	Dental Equipment and Supplies Manufacturing
339115	Ophthalmic Goods Manufacturing (pt)
334510	Electromedical and Electrotherapeutic Apparatus Manufacturing (pt)
334517	Irradiation Apparatus Manufacturing (pt)

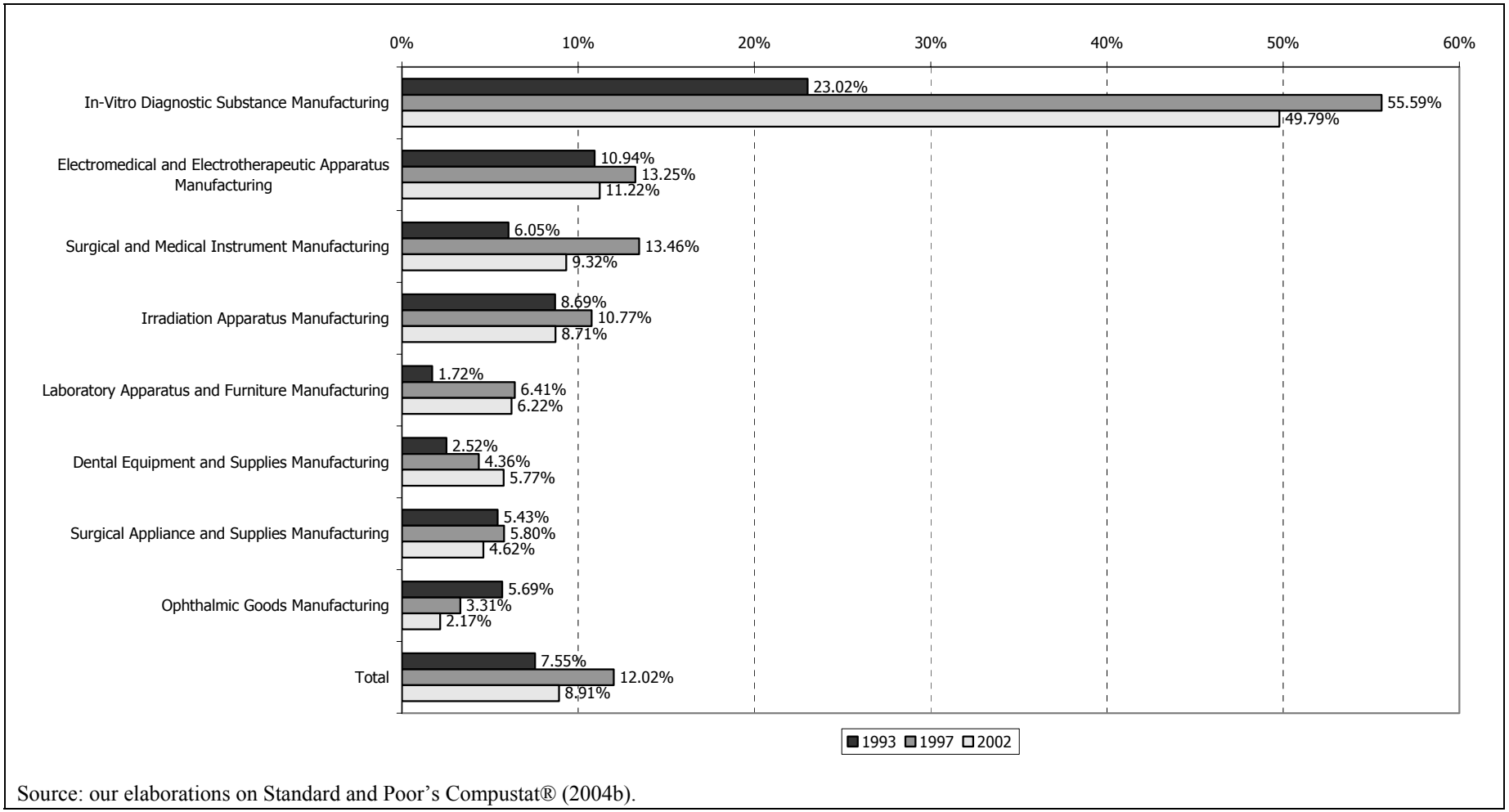
For each firm in the sample[41], we computed the share of R&D over sales and then considered the median value in three different points in time (1993, 1997, and 2002), which allows us to represent the patterns and trends of R&D intensity at the sub-market level. Results are summarised in figure 5 (see also Table A.6.3 for details).

The figures show large heterogeneity in R&D intensity between the various sub-markets. The findings are in line with the expectations: high-tech segments (in-vitro diagnostics on top of all) present the highest R&D intensity, while traditional low-tech segments (laboratory apparatus and furniture, surgical appliance and supplies) the lowest.

Trends appear clear for some sub-markets, mixed for most. As for the overall sector, the totals show an increase of the R&D intensity from in the early 1990s (when comparing 1993 to 1997), while in more recent years (1997 versus 2002), we observe a decrease in the median R&D intensity of the medical device sector.

[41] See Table A.7.2 for details about the size distribution of the firms included in the analysis. As expected, since the database cover public companies, small firms are under-represented in our sample (see Section 6).

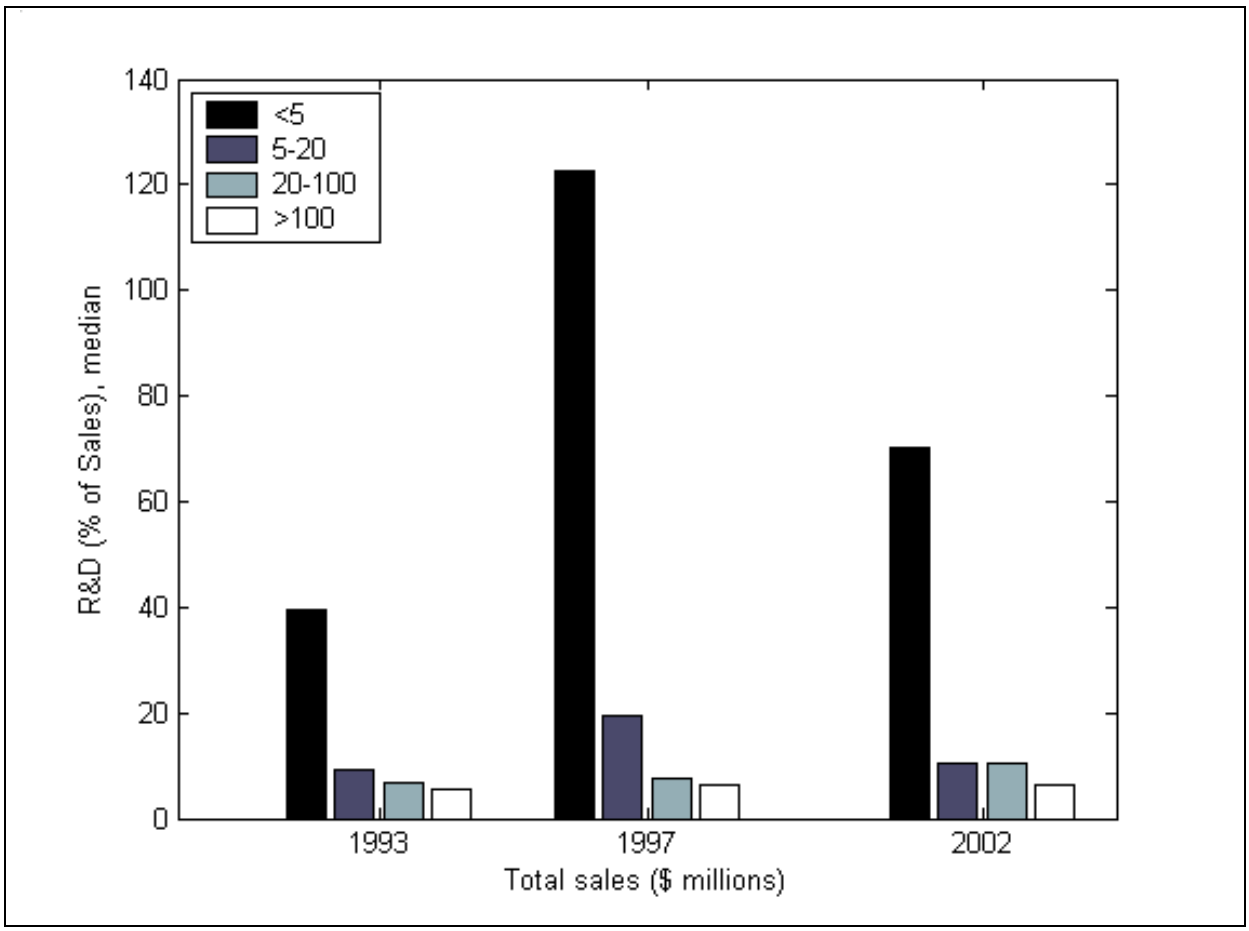
Figure 5. Median R&D intensity at the sub-market level, Compustat Companies, 1993, 1997, 2002



Source: our elaborations on Standard and Poor's Compustat® (2004b).

We then compare R&D intensity by firm size[42]. Figure 6 and figure 7 clearly show that smaller firms have a higher R&D intensity than larger ones. This is consistent with the existence of the division of innovative labour, where smaller firms are highly R&D intense and specialised in innovative activities, while the larger firms are more involved in the marketing and commercialisation of the new devices.

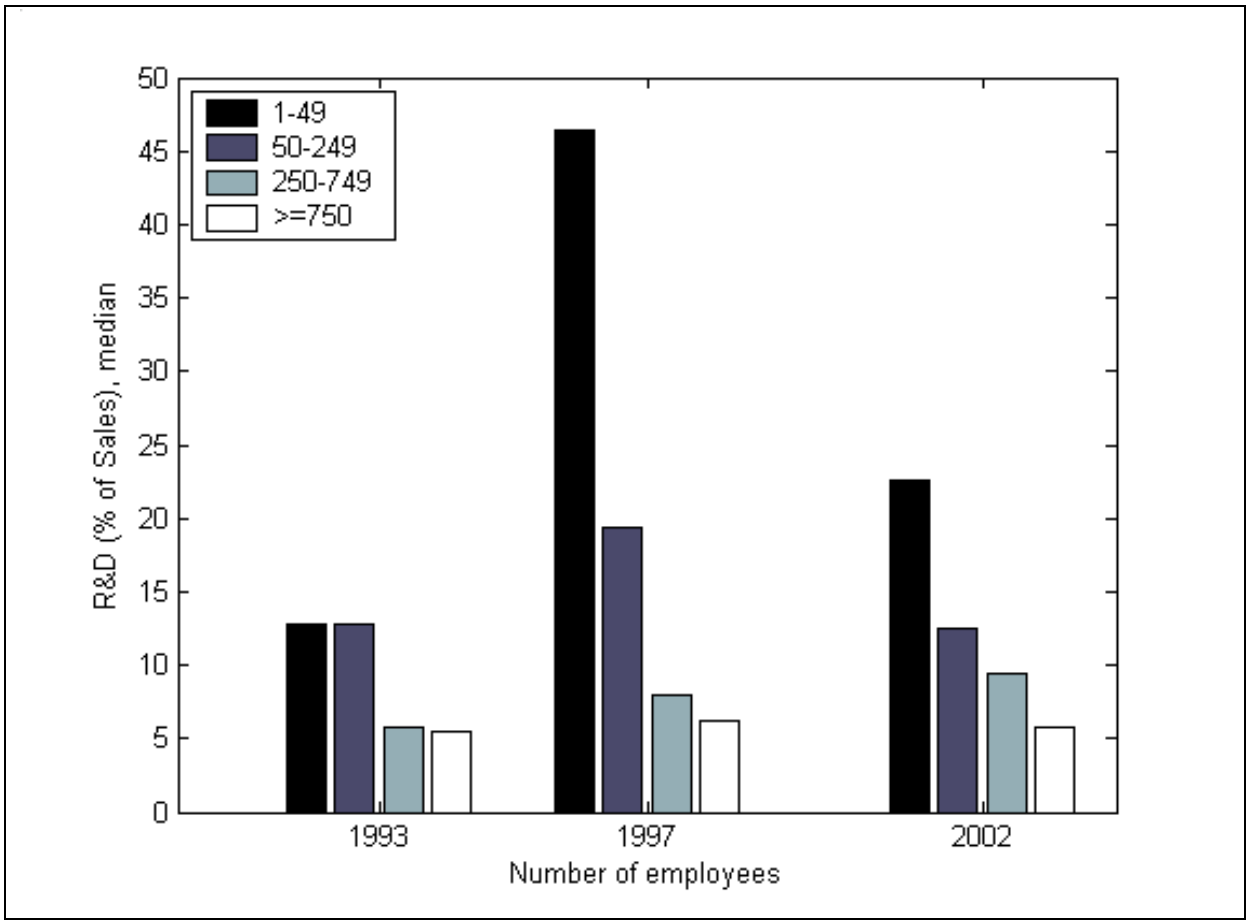
Figure 6. Distribution of R&D/Sales, by total sales ($ millions)



Source: our elaborations on Standard and Poor's Compustat® (2004b).

[42] We first classified the companies according to their size, both on the basis of sales and of the number of employees, and then we considered the median (50% percentile) for each subgroup.

Figure 7. Distribution of R&D/Sales, by number of employees



Source: our elaborations on Standard and Poor's Compustat® (2004b).

It is conventional wisdom that the division of innovative labour is at work in the pharmaceutical industry, where smaller firms are highly research intensive and have a competitive advantage in the early stage of the innovation process in drug development. Conversely, larger corporations have gained significant expertise in the later stages of the development of new innovations. It is argued in the literature that this organisation of the industry can be highly conducive to innovation performance, since it exploits the comparative advantages of larger and smaller firms in the different phases of the innovation process (Arrow, 1983). Evidence is also provided in the empirical literature supporting the existence of social advantages from this specialisation in innovative activities. The existence of a positive linkage between the probability of success of a research project and the existence of a license on the compound under development is shown in several contributions (see Arora, Gambardella, Pammolli, and Riccaboni, 2001; Danzon, Nicholson, and Pereira, 2003). Although we do not dispose of medical device research project level data, through a detailed description of the characteristics of the firms operating in the industry (mainly R&D intensity) and of the pattern of collaboration among them, we will try to understand the characteristics of the division of innovative labour, if any, in the medical device sector.

6.4 Deals and collaboration agreements

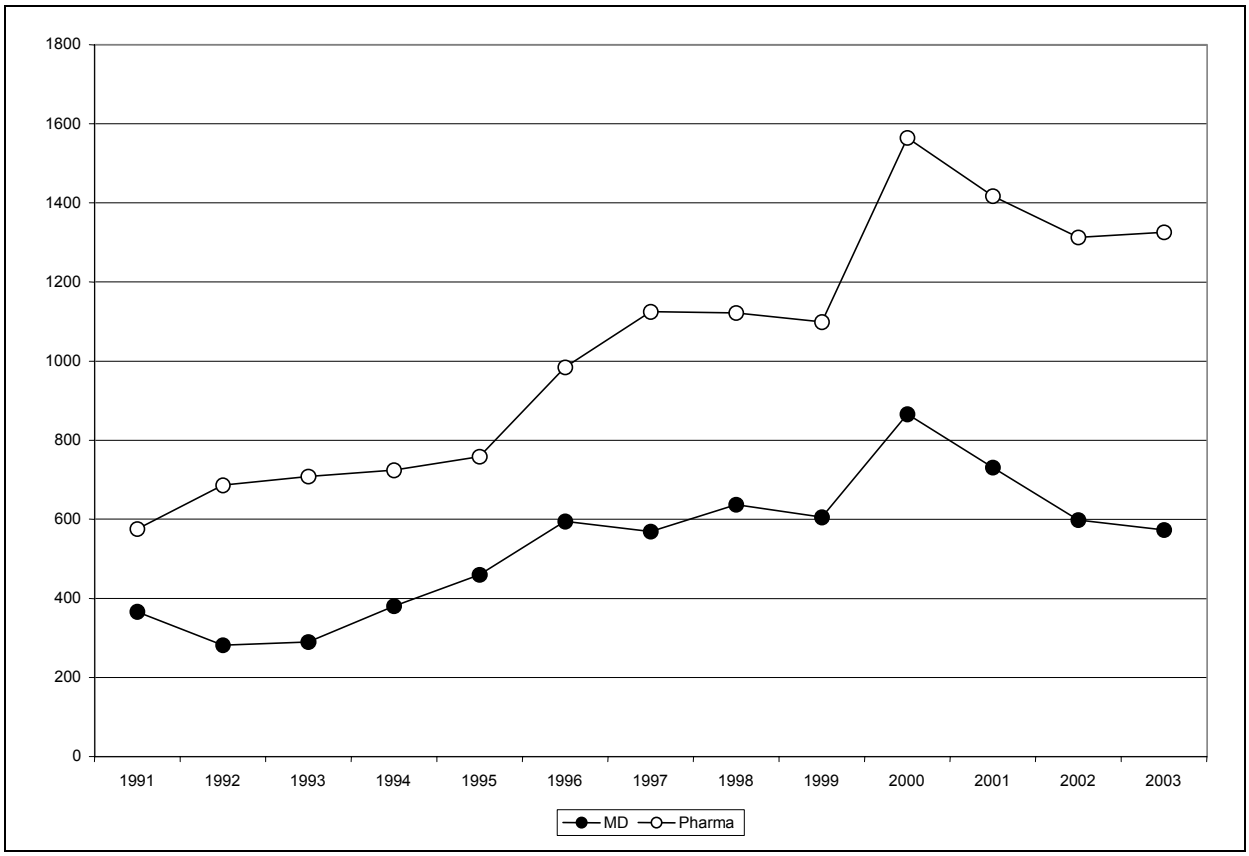
In all high-tech industries innovation fuels economic success, and medical devices are not an exception. Knowledge, which lies at the heart of the success of firms operating in a dynamic environment, can be obtained through different sources. Besides formal R&D performed within the firms, knowledge can be obtained outside the firm boundaries, through formal collaboration agreements or through the interaction among economic agents, for example between firms and basic scientists. In this section we will focus on the relevance for the medical device industry of the appropriation of knowledge that was originated outside the boundaries of the firm, either through acquisition of an existing firm, or through formal collaboration agreements. In doing so, we aim at further exploring the division of innovative labour in the medical device industry.

ATAdb (ATA, 2004), covering the most relevant deals on a worldwide level, reports a total of 6,953 deals for medical devices from year 1991 to 2003. The organisations involved in the deals were classified into public/private and we distinguish biotech firms (considering first tier biotech separately), public research organisations, large pharmaceutical firms and other firms, according to their main technology.

Figure 8 graphically depicts the evolution of the total number of deals among firms in the medical device industry over time and compares this dynamics with the evolution of the total number of deals in the pharmaceutical and biotechnology industry.

The series describing the number of deals in the medical device and pharmaceutical industries proceed paired: the total number of deals in both industries decreased sharply starting from 2000, after a steep rise. In 2003 the decline stops, and the figures are roughly equal to the ones in 2002. However, the number of deals is significantly lower in medical devices when compared to the pharmaceutical industry.

Figure 8. Total number of medical device and Pharmaceutical deals, 1991-2003



Source: ATA (2004).

Table 9 distinguishes between acquisitions (total or partial), alliances (joint ventures, R&D and marketing agreements, product acquisitions), and financing types of collaboration. Quite different purposes and arrangements characterise the acquisition, licensing and financing agreements. Therefore, we will in turn analyse the dynamics of acquisitions, both in terms of numbers and value of the acquisitions, and the patterns of R&D licensing agreements.

Table 9. Number of medical device and Pharmaceutical collaborations, by deal type

	Medical Device Collaborations				Pharmaceutical Collaborations			
Year	Total	Acquisition (%)	Alliance (%)	Financing (%)	Total	Acquisition (%)	Alliance (%)	Financing (%)
1991	366	26.50	41.53	31.97	621	13.53	59.42	27.05
1992	282	28.72	40.43	30.85	712	13.06	63.76	23.17
1993	290	25.17	47.24	27.59	728	8.93	59.75	31.32
1994	381	28.87	49.08	22.05	753	10.89	65.21	23.90
1995	460	29.78	43.26	26.96	784	14.67	59.57	25.77
1996	595	21.18	46.39	32.44	1,025	9.46	60.68	29.85
1997	569	17.22	53.95	28.82	1,157	8.47	63.79	27.74

	Medical Device Collaborations				Pharmaceutical Collaborations			
Year	Total	Acquisition (%)	Alliance (%)	Financing (%)	Total	Acquisition (%)	Alliance (%)	Financing (%)
1998	637	19.94	51.02	29.04	1,190	8.57	66.97	24.45
1999	605	19.34	51.24	29.42	1,143	10.67	63.52	25.81
2000	866	18.59	42.96	38.45	1,662	10.53	54.09	35.38
2001	731	15.46	50.34	34.20	1,464	10.31	60.45	29.23
2002	598	18.06	46.66	35.28	1,415	8.76	64.45	26.78
2003	573	21.47	37.52	41.01	1,421	9.50	55.45	35.05

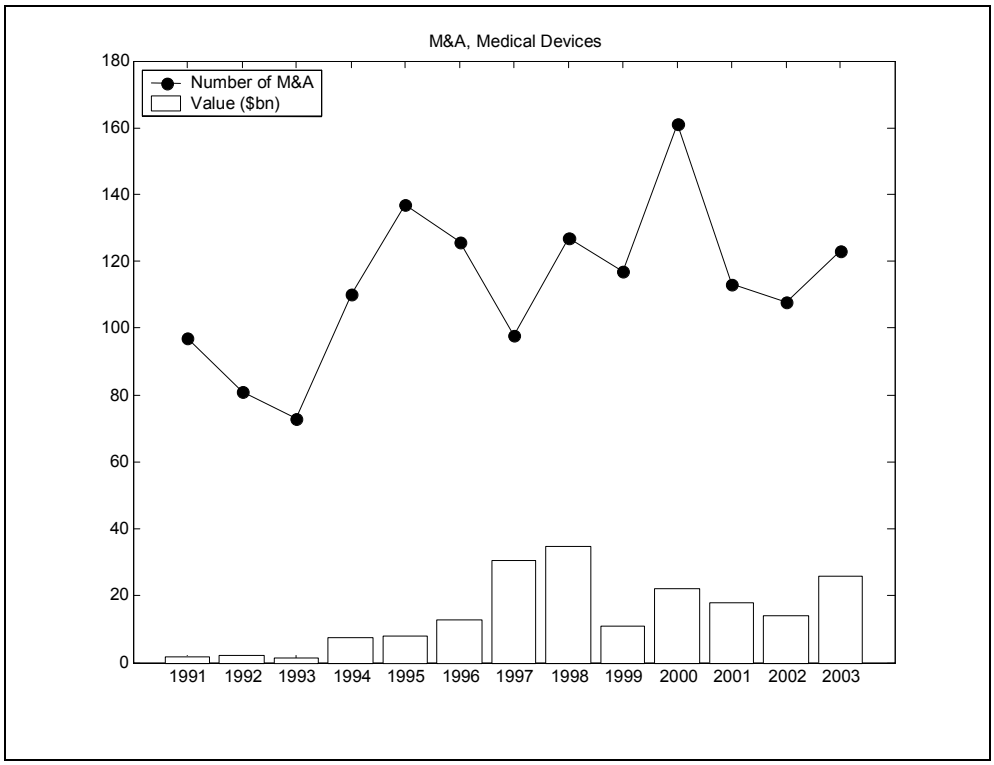
Source: ATA (2004).

In relative terms, acquisitions play a larger role in medical devices as compared to pharmaceuticals, even though the share of medical device acquisitions has declined from 26.50 percent in 1991 to 21.47 percent in 2003 (increasing from 18.06 percent in 2002).

Figure 9 and figure 10 report the number and deal value of acquisitions respectively in the medical device and pharmaceutical industries over the period 1991-2003. A peak of acquisitions has been registered in 1997 and 1998 in the medical device industry, which however does not correspond to a peak in deal value. This circumstance means that the average value of acquisition has been reduced in these years.

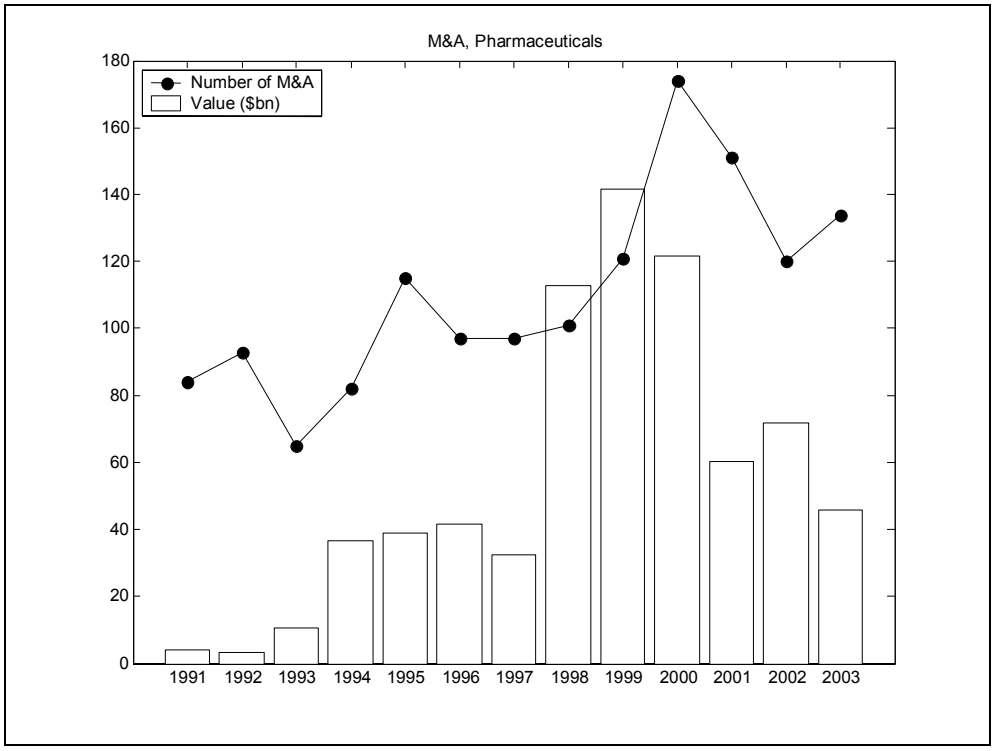
When compared to the acquisitions within the pharmaceutical industry, both the total value and the number of agreements in the medical device industry is significantly lower. Also, M&A are characterised by a lower average value in the medical device industry as compared to the pharmaceutical industry.

Figure 9 M&A number and value, medical devices



Source: ATA (2004).

Figure 10. M&A number and value, Pharmaceuticals



Source: ATA (2004).

Table 10 analyses the nationality of the institutions involved in the medical device acquisition agreements, reporting the number and the average value of the acquisitions involving US, European, and Japanese institutions.
It is interesting to note the low level of M&A within the European boundaries coupled with a high number of US-Europe acquisitions. Also, the average value of US-Europe acquisition is the largest for the medical device agreements.

Table 10. Number and average value of acquisition agreements, medical devices, 1991-2003

	Number			Avg. Value		
	US	**Europe**	**Japan**	**US**	**Europe**	**Japan**
US	835			125.10		
Europe	429	55		165.59	152.08	
Japan	16	2	0	46.52	85.00	--

Source: ATA (2004).

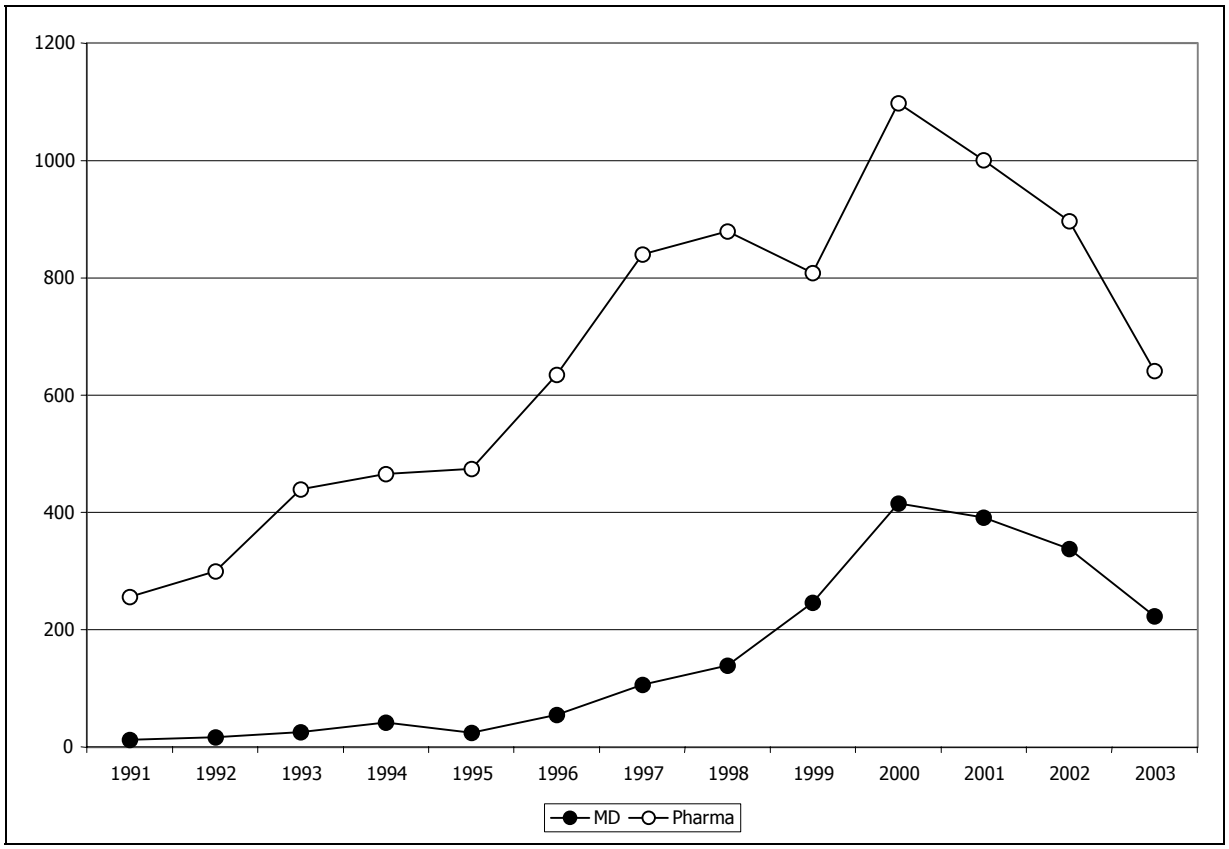
Next, our interest is in the patterns and characteristics of the R&D alliances.

We selected all the deals with R&D content where it was possible to distinguish the licensee from the licensor. In the case of one licensor and multiple licensees, we considered different deals for each licensee. The final sample of deals signed between 1991 and 2003 is composed of 2,112 licensing agreements.

Figure 11 reports the evolution over time of the number of subscribed licensing agreements, comparing medical devices and pharmaceuticals. The pattern for both series is similar to that seen above, peaking in 2000 and then decreasing[43].

[43] The decrease in later years is contrasted to the sharp increase of patent co-assignment during the period 2000-2003. However patent co-assignment is a particularly strong form of collaboration among firms, where they share the intellectual property right spanning from the research. In addition, licensing agreements are signed at different stages of the innovation process.

Figure 11. Evolution over time, R&D licensing agreements, medical devices and pharmaceuticals



Source: ATA (2004).

Figure 12 graphically depicts the network of R&D licensing agreements classifying the originator and the developer (respectively the licensor and the licensee) according to the nationality of the organisations. From the figures, it is possible to understand the size of the R&D network of the institutions in each country and their preferred partners[44].

Only ties involving more than 3 deals between countries are reported and isolated nodes are deleted from the picture, after imposing this filter. The size of the lines connecting country X and Y is proportional to the total number of deals involving the two countries, and the size of each node is proportional to the number of out-licensing agreements it subscribed (within-country licensing agreements are considered).

The dominance of the US in this network is striking. The US has a strong world dominance both as originator and as developer of licensing agreements. US organisations originated 75 percent of the deals in the network and developed 71 percent. Moreover, the picture reveals the presence of a large North American network. More than 80 percent of the licenses originated (developed) by US institutions are developed (originated) in US and Canada (see also Table A.6.4).

On the contrary, Europe does not constitute a self-standing network: a large share of the projects originated/developed in Europe is then developed/originated by institutions in the

[44] Detailed statistics are reported in Table A.7.4 in Annex 7.

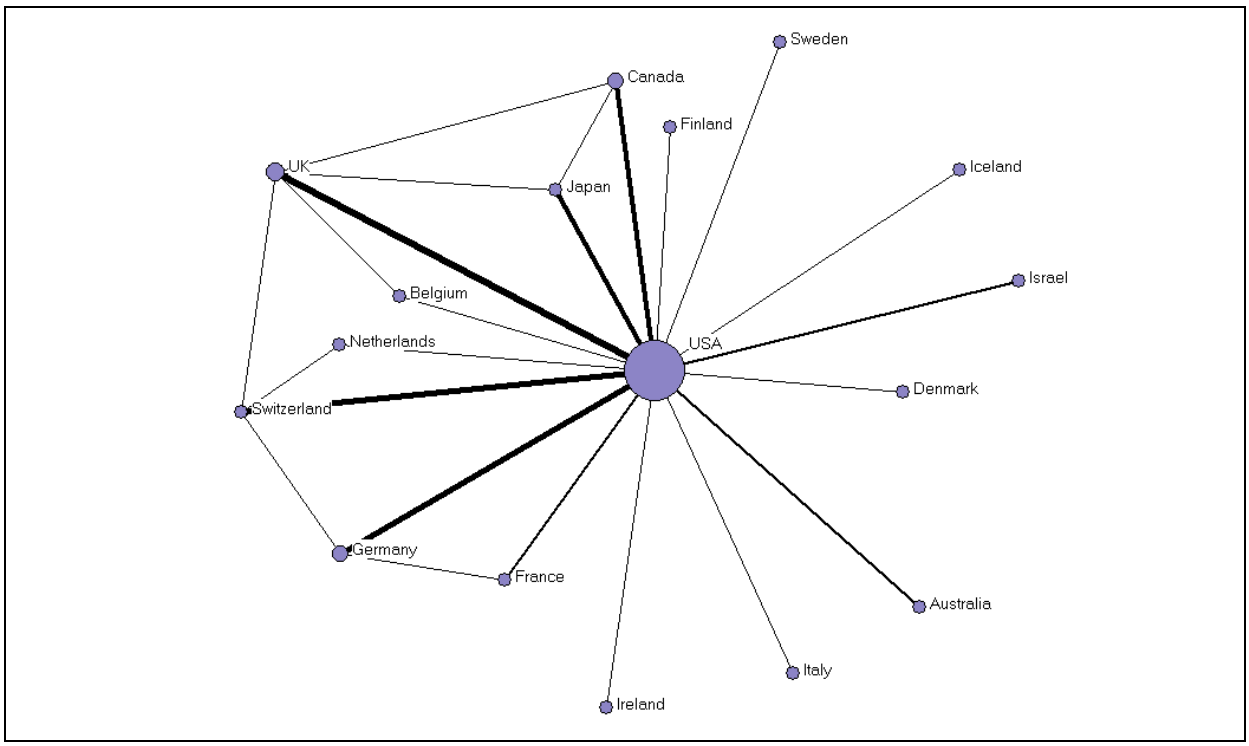
US. Significant relationships are present between Germany and France on the one side and between the UK and Belgium on the other. However, the linkage with the US appears to be stronger than the linkages between European countries.

As for Japan, the national Japanese network is almost non-existent (a low share of deals originated by a Japanese institution has a national partner). The preferred partner is usually the US, and no significant interaction takes place with Europe, the only exception being the UK.

Moreover, Japan is the country with the largest negative difference between originated and developed projects, meaning that this country relies heavily on other countries (mainly the US) as a source of useful medical and in vitro technologies. On the other side, the US has always a large and positive difference.

Overall, the centrality of the US network emerges both in terms of number of deals originated and developed, and as preferred partner of European and Japanese institutions.

Figure 12. Network of medical device R&D licensing agreements



Source: ATA (2004).

It is interesting to compare the information about the flow of products (analysed in Section 6) with the information about the flow of technology as described by the R&D licensing agreements analysed in this section[45]. For each country in the analysis, we linked the indicator of "trade balance" (defined in section 5 as the ratio of medical device export to total medical device trade), to an analogous indicator of "R&D balance" computed as the ratio of R&D out-licensing agreements over the total number of agreements (the sum of in-licensing and out-licensing agreements). A value of the index higher (lower) than 0.5 indicates a positive

[45] Since the in vitro diagnostics industry is not included in the international trade flow analysis, it will be excluded also in the analysis that follows.

(negative) R&D balance: countries with a value of the index lower than 0.5 are net importers of technology (i.e. the number of R&D in-licensing agreements is higher than the number of R&D out-licensing agreements), while the reverse is true if the index is higher than 0.5.

In Figure 13 we represent the two indexes jointly (product and technology "trade balance").

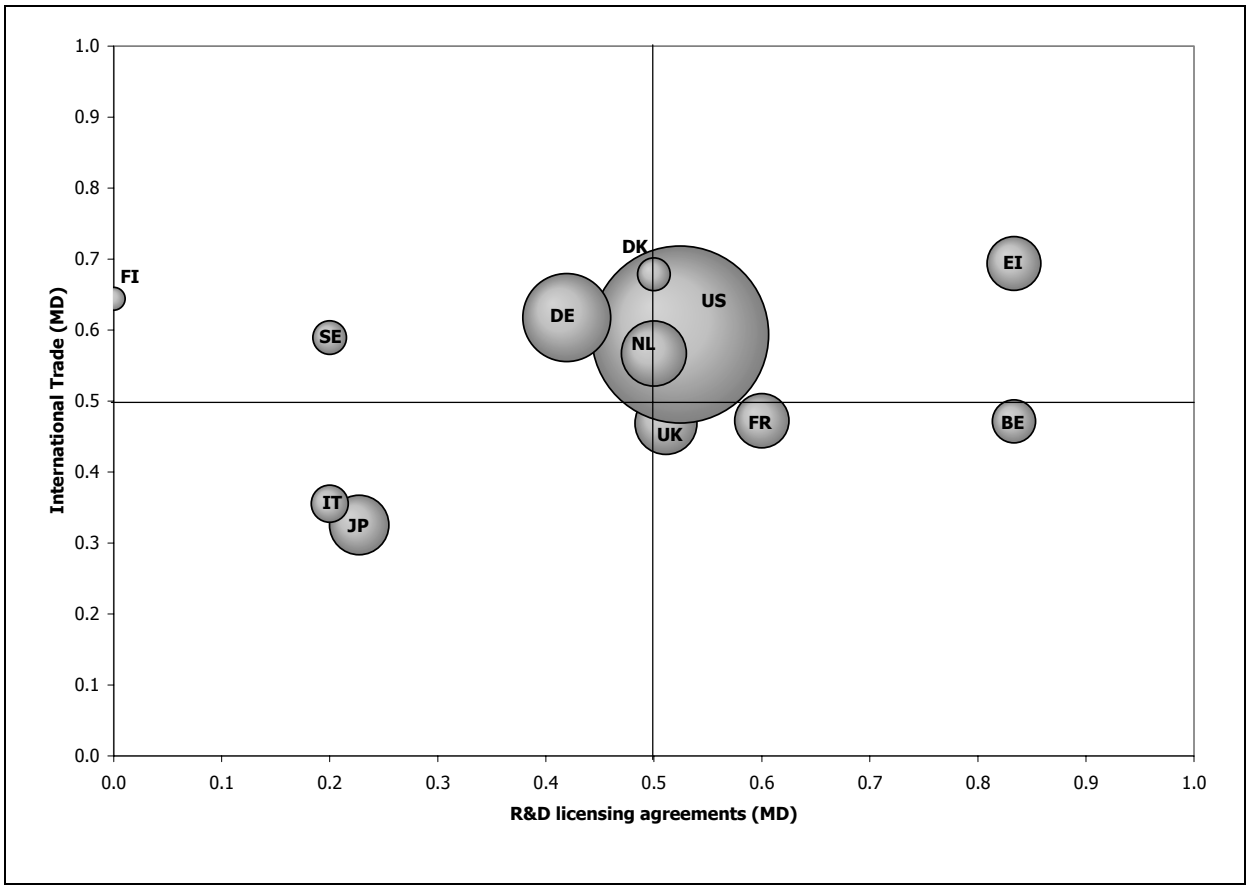
The x-coordinate represents the technology "trade balance" computed on the basis of the licensing agreements, while the y-coordinate represents the product "trade balance" as computed in Section 6. The size of each country is proportional to its number of out-licensing agreements and to the value of its exports.

The top left panel of the figure contains countries that are exporters of both products and technology, therefore in a strong competitive position on the international market, both on the R&D and on the product sides. These are the US and Ireland.

The lower right panel contains countries that are importers of both technologies and products. This panel contains Japan and Italy. Japan is indeed a net importer of both technology and products: both the product and the R&D "trade balance" have a value which is lower than 0.5 suggesting the fact that imports of both technology (through R&D alliances) and products are larger than the respective exports.

The other quadrants contain countries that are importers in one dimension (product or technology) and exporters in the other one.

Figure 13. R&D and product international "trade balance"



Source: our elaborations on Eurostat (2004b), ATA (2004).

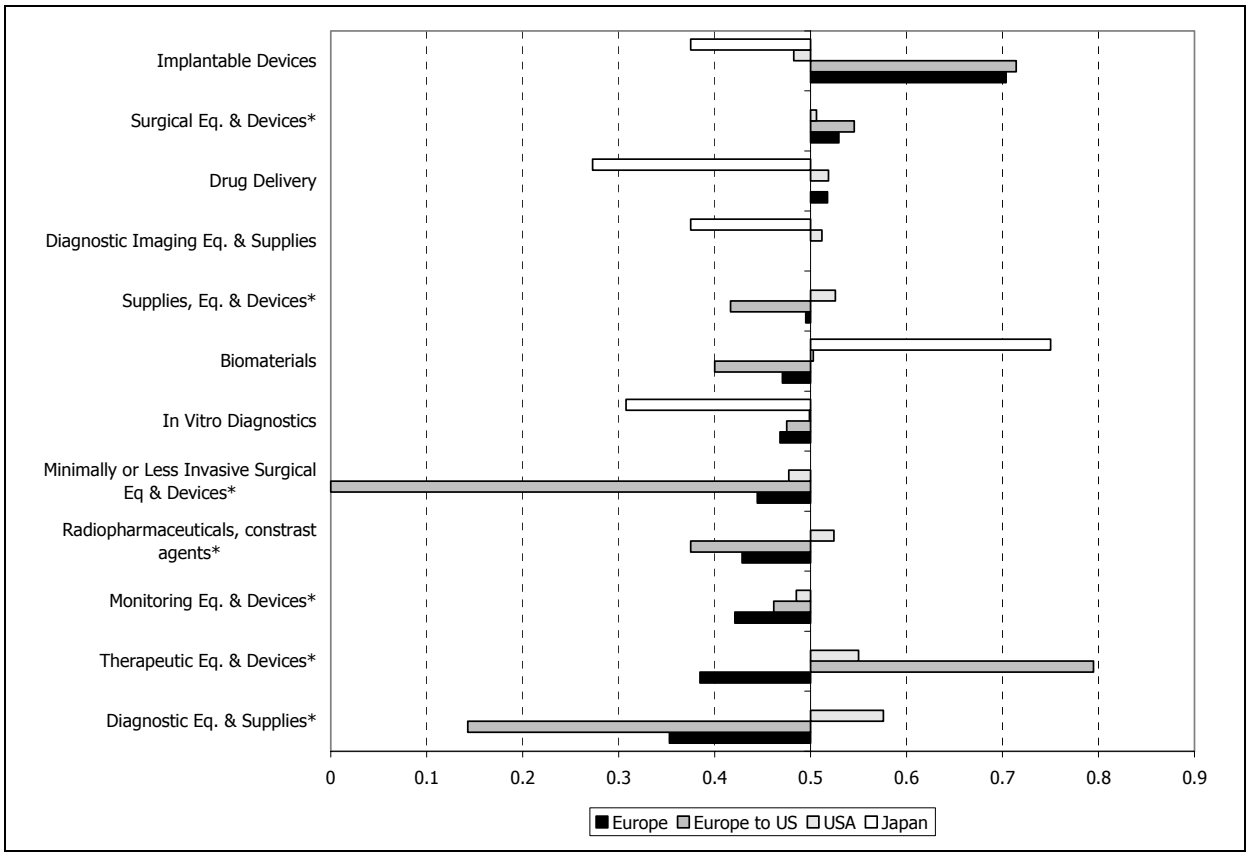
Given the high heterogeneity of the medical device industry, we also consider a more disaggregated level, and we analyse specific sub-markets comparing the in-licensing agreements to out-licensing agreements related to specific technologies.

Unfortunately, the classification system employed in the ATAdb (ATA, 2004) for R&D deals is not easily reconciled with the classification systems employed for the classification of products. Therefore, extreme care is needed when comparing trade and technology flows at the sub-market level.

Figure 14 reports the index previously described for Europe, US and Japanese firms. The diagram also considers the index computed for Europe taking into account the international technology flow from and to the US only. The European competitive position varies widely when considering specific sub-markets.

European countries are net exporters of technology related to implantable devices, surgical equipment and devices (excluding minimally or less invasive surgical equipment and devices), and for drug delivery R&D alliances. When considering the therapeutic equipment and devices, Europe is a net importer. However, the technology balance with the US is positive (the index is higher than 0.5). The US has a technology trade balance always close to zero. Japan is the major net exporter of R&D alliances on biomaterials.

Figure 14. Technology flows for selected sub-markets, medical device



Source: ATA (2004).

6.5 Innovative output: patents, publications, and new product introductions

In this section we analyse the output side of innovative activity looking both at patents and publications related to the medical device industry. In particular, by using the information on the location of the assignees (and inventors) in patents and on the affiliation in the publications, we will characterise the location of R&D activities within the industry.

The nature of the innovation process in medical devices does not always lead to patentable claims. The basic principle behind innovation in medical devices can be patentable, but specific devices usually are not, since it is possible to design a device for a given application in a number of different ways (see Kahn, 1991). Therefore, taking into account both patents and publications, we aim at providing a more complete picture of the innovative effort in R&D.

When using simple patent counts to measure the innovative performance of firms and institutions, the fact that "*the quality of the underlying innovation varies widely from patent to patent*" (Scherer, 1965) is not taken into account. For this reason, citations by subsequent patents, a piece of information nowadays easily available from patent documents, have been extensively used to proxy the impact of a patented innovation. Subsequent patent citations indicate that the cited patent has opened the way to a line of innovations, and it is therefore significant, at least in a technological sense.

The first empirical work that assessed a linkage between the number of citations received by a patent and its economic significance analysed computed tomography scanners (CT). Trajtenberg (1990) provides evidence that the number of subsequent citations received by patents are positively correlated with their social surplus using information about citations to CT patents in the US and estimates of the associated social surplus[46]. It is also hinted that, since patents and patent citations are the result of the action of profit-seeking agents, citations can be informative also of the economic success of the innovations.

This suggestion has been confirmed by surveys (Harhoff, Narin, Scherer, Vopel, 1999; Jaffe, Trajtenberg, Fogarty, 2000) and empirical work analysing the probability of renewal and of litigation of patents (see Lanjouw and Schankerman, 1999). Due to the high costs involved in litigation and renewal procedures, these events can be informative of the private value of the associated patented innovations.

In our analysis, besides simple patent counts, we will also consider patent citations, in order to take into account the technological and economic impact of the patented innovations.

Similarly, simple publication counts do not take into account that the quality of published research may vary widely. Therefore, we used the impact factor of journals to calculate a weighted count of publications.

The first step in the analysis consisted in the identification of the patents and publications in the medical device sector.

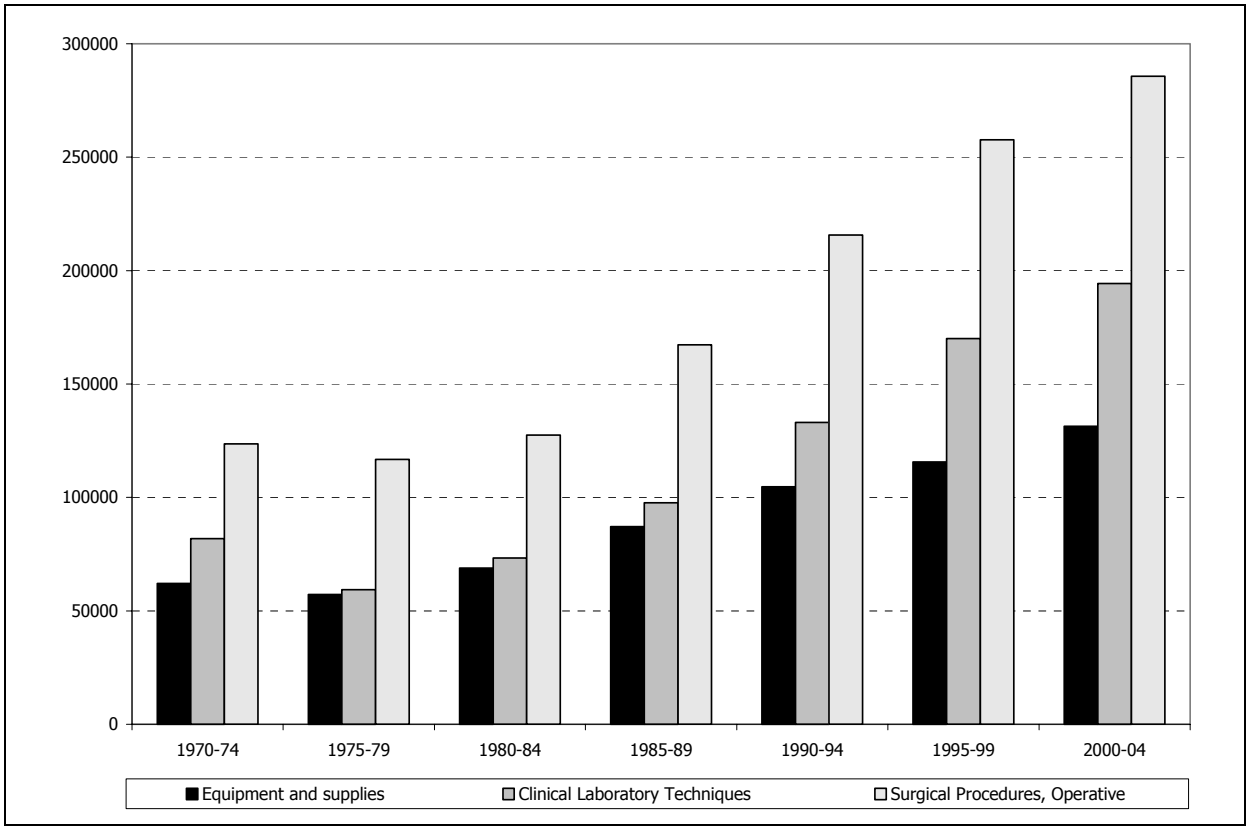
As for publications, we used the MeSH database from Pubmed to identify publications pertaining to the medical device sector. We considered the more than 600,000 publications

[46] The author used information about sales to hospital, and attributes and prices of all CT scanners marketed in the US from 1973 (corresponding to the inception of CT) to 1982. He applied a multinomial logit model to data on sales per brand and on their attributes and prices to estimate the parameters of the demand function and, under some restrictions, of the corresponding utility function. The social gain in each year is obtained by comparing the consumer and producer surplus in two subsequent periods (see also Trajtenberg, 1989).

related to the equipment, supplies, apparatus, and instruments used in diagnostic, surgical, therapeutic, scientific, and experimental procedures (Equipment and Supplies).

Figure 15 reports the evolution of publications over time. We also include the trends in the number of publications related to clinical laboratory techniques and surgical procedures. The number of publications in all the three categories considered has increased over time.

Figure 15. Trends in the number of publications, medical devices



Source: Pubmed.

ATA (2004) was employed to analyse the publication data at a more detailed level.

In order to identify medical device patents, we selected patents classified into specific categories within the International Patent Classification (IPC) system and we searched specific words within the abstract of the patent (ATA, 2004).

In particular, within the broad class A (Human Necessities), we focus on the class A6, i.e. Health, Amusement, looking more deeply at the patent classified within A61 (Medical or Veterinary Science; Hygiene). We considered the patents with main IPC in the following classes[47]:

- A61B: Diagnosis; Surgery; Identification.

[47] We did not consider the classes A61C (dentistry; oral or dental hygiene), and A61H (physical therapy apparatus), which are nonetheless a small share of the health patents (see Lichtenberg and Virabhak, 2003).

- A61F: filters implantable into blood vessels; Prostheses; Orthopaedic, nursing or contraceptive devices; Fomentation; Treatment or protection of eyes or ears; Bandages, dressings or absorbent pads; First-aid kits (excluding classes A61F 13, 15, and 17).
- A61M: devices for introducing media into, or onto, the body; Devices for transducing body media or for taking media from the body; Devices for producing or ending sleep or stupor.
- A61N: electrotherapy; Magnetotherapy; Radiation therapy; Ultrasound therapy.

Finally, we included the devices for in vitro diagnostics in our sample. These have been selected using the information contained in the abstract of the patent and in the IPC that helped us in discarding the patent where "in vitro" technologies were applied to targets other than human/biological essays.

In the analysis that follows we only considered the (about) 120,000 medical device patents registered in the US.

We are confident that the analysis conducted here provides a satisfactory picture of the innovative activities in the medical device industry: given the size and the relevance of the US market, most innovations are also patented in the US.

Figure 16 compares the evolution of the number of patents in the medical device industry (i.e. in the classes we considered) and the Pharmaceutical industry[48] over time, from 1980 to 2003. The two series proceed paired: the number of medical device patents increased smoothly up to the mid-1990s; then we observe a few years where the number of granted patents stayed approximately constant, and then the number of granted patents increased sharply over the 1990s. In recent years, the increase has slowed down and the number of both medical device and pharmaceutical patents remained approximately constant.

In order to analyse the pattern of location of R&D activities around the world, we also considered the nationality of the assignee(s) owing the property right[49] and the country of the affiliation in publications.

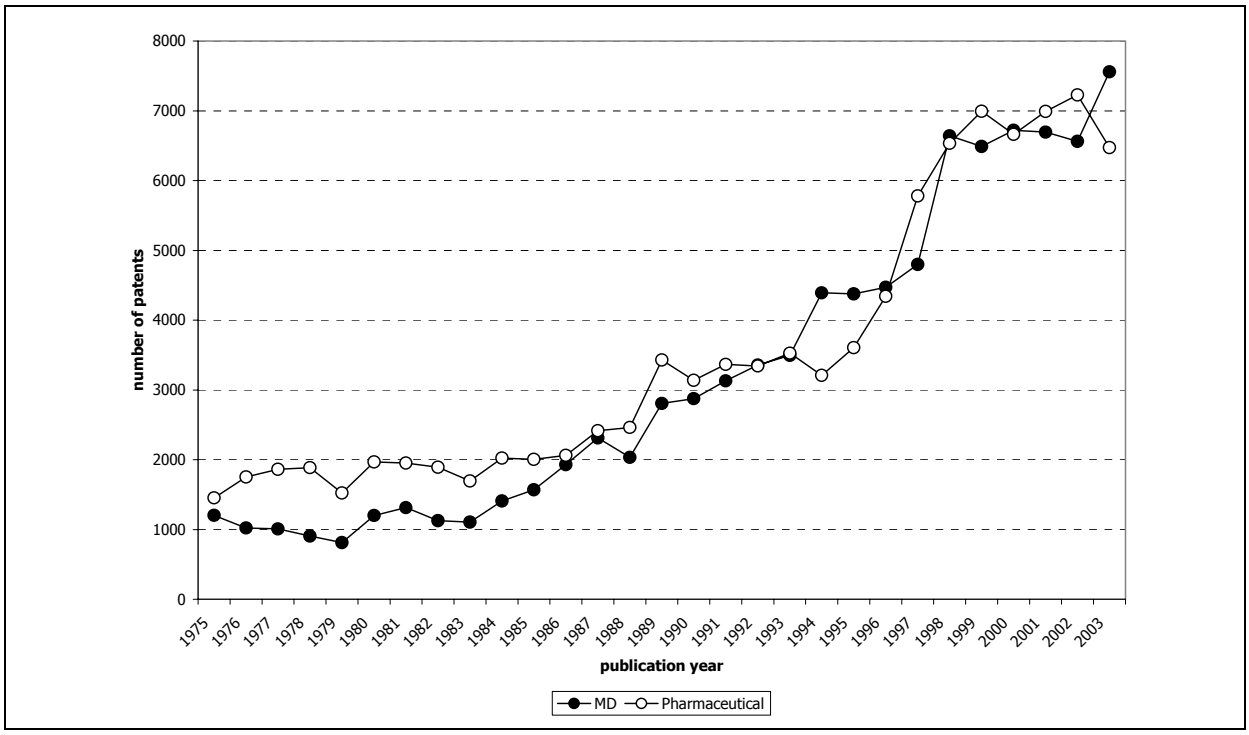
Figure 17 reports the evolution of medical device patents, distinguishing US and non-US assignees. Both series increase over time, and a large share of patents is granted to US institutions. This share has remained approximately constant over the latest years (see the box in Figure 17)[50].

[48] Analogously to the MD patent selection, pharmaceutical patents have been selected according to the IPC classification. Particularly, we considered the patents with main IPC in the classes A61K and A01N (see Lanjouw and Cockburn, 2001).

[49] We also considered the nationality of the first inventor listed in the patent. Results do not change substantially (see Table A.7.5). When analysing the assignee, in order to consider the nationality of all the organizations involved in the invention process, we weighted the count of patents by the share of the assignees in the patent that were located in the country considered. For example, consider a patent with ten inventors, three of which from the US and seven from UK. When counting the patents for US, we considered this particular patent assigning 0.3 to the US and 0.7 to the UK.

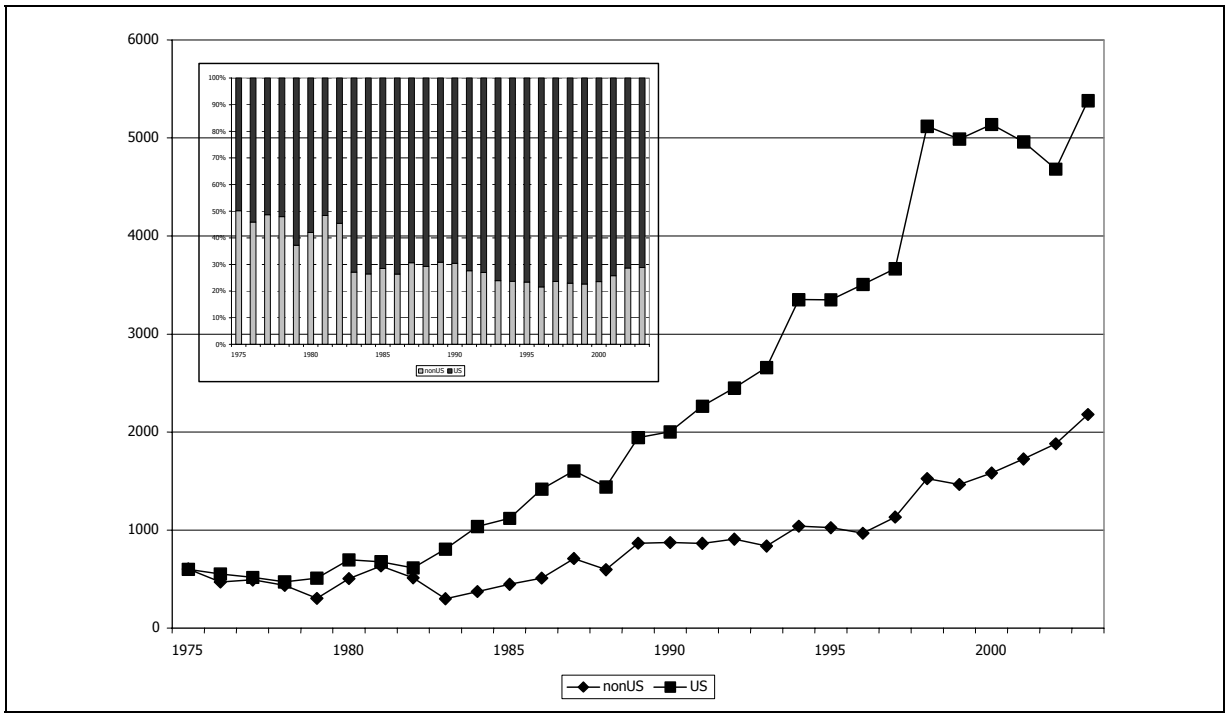
[50] The analysis might be biased toward US corporations, due to the so called "home advantage bias", i.e. the fact that companies first file a patent in their home country. The literature has proposed the use of the triadic patent families to overcome this bias (see Dernis and Kahn, 2004). however, it is a fact that US corporations have a stronger effort in health patents (Lichtenberg and Virabhak, 2003).

Figure 16. Evolution of publications and US patents, 1975-2003, medical devices and pharmaceuticals



Source: ATA (2004).

Figure 17. Evolution of US patents (in the box: shares), 1975-2003, medical devices, by nationality of assignee



Source: ATA (2004).

Table 11 digs further into this issue and shows the number and the share of the patents classified according to the nationality of the assignee over the period 1974-2003[51].

We consider the location of the assignee(s) in patents and the affiliation of the corresponding author in the case of publications, which indicates the location of the research laboratory that set forth the innovation. As already explained, we weighted the count of patent by the share of the assignees in the patent that were located in the country considered.

Results do not change substantially looking at patents or at publications. In both cases, the data on the location of innovative activities shows the comparative advantage of the US over the European countries in attracting research in the medical device sector (see Table 11).

Since the compared countries differ greatly in terms of size, we considered the number of patents/publication per 100,000 inhabitants, in order to control for bias due to country size. It would be preferable to standardise the patent and publication counts using the number of R&D personnel employed in the medical device industry. Unfortunately we have no such information available.

Finally, our database reports the information about the number of forward citations received by each patent and the impact factor of each publication. Patent counts and publication counts are an imperfect measure of the innovative output, due to the fact that patents differ greatly in terms of value. Moreover, publications in different journals have in fact a different scientific content. Therefore, taking into consideration the number of forward citations and the impact factor of publications allow us to take into account the "importance" of the innovations. As already explained, the number of citations tends to be correlated with the technological and economic value of a patent: the higher the number of citations received, the higher the impact of the cited patent. Consequently, patent citations provide a better measure of the technological and economic potential value of innovative activities than patent counts. An analogous argument holds for the impact factor of publications, that can be interpreted as a measure of the quality and relevance of the firm or country innovative activities. Table 11 reports the number of patent citations and the total impact factor, by nationality of patent assignee.

US dominance in the medical device sector turns out to be even stronger than it appears from patent counts data. The share of citations to patents assigned to US institutions suggests that on average these have a relatively greater impact on future innovative activity. European countries and also Japan lag far behind, and overall those countries experience a decline in their relative position in terms of patenting activity. The reverse is true when looking at publications (see Table A.6.7).

The result is also confirmed if we consider the average number of citations received and the average impact factor of publications, taken as a proxy for the "importance" of the research in the countries analysed (see Figure 18).

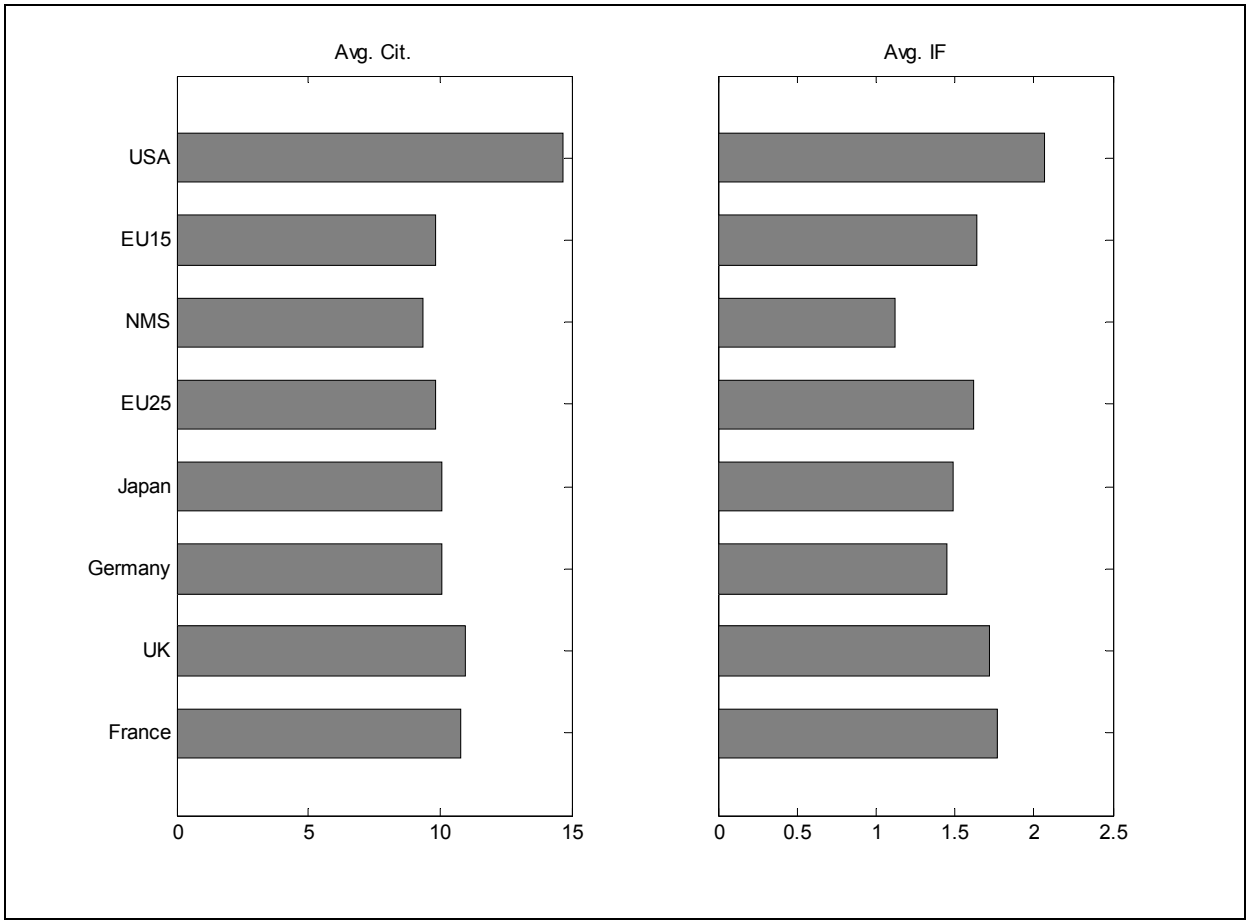
[51] We also considered the patents classified according to the nationality of the first inventor. No significant difference emerges when considering assignees or inventors. Also when considering inventors, the dominance of US is striking. Patents from US inventors account for over 70 percent of the total over the entire period under analysis. The second Country is Japan, that had a share of 5.5 percent in 2003. The first four EU countries, Germany, France, UK and Sweden, account for 10 percent. No significant trend or pattern in the relative position of innovators is shown (see Table A.7.5 for detailed statistics).

Table 11. US Patents and Publications, by nationality of assignee, 1974-2003

	Patents (1974-2003)						Publications (1974-2003)					
	Count	%	Pat. per 100.000 ab	Citations	%	Cit. per 100.000 ab	Count	%	Publ. per 100.000 ab	IF	%	IF per 100.000 ab
US	68389	74.60	27.80	1002484	81.43	407.53	99801	37.96	40.57	206604	44.77	83.99
EU15	11340	12.37	3.13	111260	9.04	30.68	94182	35.83	25.97	154128	33.40	42.51
NMS	125	0.14	0.17	1165	0.09	1.59	2311	0.88	3.14	2588	0.56	3.52
EU25	11464	12.51	2.63	112425	9.13	25.78	96493	36.70	22.13	156715	33.96	35.94
Japan	6323	6.90	5.23	63460	5.15	52.46	21352	8.12	17.65	31725	6.88	26.23
Germany	4255	4.64	5.35	42796	3.48	53.77	21725	8.26	27.30	31389	6.80	39.44
UK	1734	1.89	3.03	19028	1.55	33.23	22595	8.59	39.46	38822	8.41	67.80
France	1691	1.84	3.03	18236	1.48	32.64	10811	4.11	19.35	19160	4.15	34.30
Switzerland	1230	1.34	18.41	14112	1.15	211.24	4812	1.83	72.03	7549	1.64	113.00
Canada	1132	1.23	4.20	12057	0.98	44.75	9344	3.55	34.68	18717	4.06	69.46
Sweden	1119	1.22	13.15	9300	0.76	109.22	6016	2.29	70.66	9436	2.05	110.83
Israel	812	0.89	17.42	7314	0.59	156.84	2685	1.02	57.58	4670	1.01	100.13
Netherlands	828	0.90	5.61	6703	0.54	45.38	6803	2.59	46.06	13810	2.99	93.50
Australia	550	0.60	3.35	6093	0.49	37.06	5913	2.25	35.96	9456	2.05	57.51
Italy	612	0.67	1.08	6068	0.49	10.70	8264	3.14	14.57	13259	2.87	23.38
Total	89901	98.06		1217945	98.93		240400	91.44		435436	94.37	
Total (a)	91675	100.00		1231154	100.00		549208	100.00		844627	100.00	
Unknown (b)	2691			47575			286314			383193		

Source: ATA (2004)

Figure 18: Average citations and average impact factor, by nationality of assignee/affiliation



Source: ATA (2004).

The importance of patents, as measured by the number of citations received, and that of publications, as measured by the impact factor, is lower for the European countries and Japan with respect to the US.

At a more disaggregated level, we take into account the city of the assignee in patents or of the affiliation in publications. Table 12 reports the number and importance of publications and patents of the most productive cities, where we only considered patents and publications published from 1980. In particular, we selected the set of cities that ranked among the top 15 either in terms of the citations received by their patents, or in terms of the impact factor of their publication. Given the results of the analysis at a national level, it is not surprising that the large majority of the top cities are located in the US. To get a picture also of the position of European cities, we included in the table the main European cities.

Table 12. Top cities in terms of importance of patents and publications, 1980-2003

City	Rank Pat.	Rank Publ.	Patents				Publications			
			N	% N	Cit.	% Cit	N	% N	IF	% IF
Minneapolis, MN	1	19	2436	5.35	39882	6.60	1518	0.70	3419	0.89
Tokyo	2	5	3087	6.78	30456	5.04	4793	2.23	6565	1.70
Sunnyvale, CA	3	585	884	1.94	16957	2.80	42	0.02	65	0.02
New York, NY	4	1	1046	2.30	15477	2.56	7971	3.70	16725	4.33
Saint Paul, MN	5	137	1318	2.89	15597	2.58	304	0.14	514	0.13
Palo Alto, CA	7	136	906	1.99	13988	2.31	236	0.11	526	0.14
Norwalk, CT	8	1266	886	1.95	13516	2.24	6	0.00	14	0.00
Mt. View, CA	9	601	710	1.56	12852	2.13	36	0.02	62	0.02
Deerfield, IL	10	2165	679	1.49	12124	2.01	9	0.00	5	0.00
Menlo Park, CA	11	313	534	1.17	11902	1.97	52	0.02	167	0.04
Santa Clara, CA	12	561	778	1.71	11693	1.93	29	0.01	71	0.02
Boston, MA	14	3	666	1.46	9886	1.63	5077	2.36	13891	3.60
Murray Hill, NJ	15	427	393	0.86	9377	1.55	16	0.01	108	0.03
London	34	2	433	0.95	4634	0.77	7359	3.42	14286	3.70
Seattle, WA	39	12	271	0.60	3802	0.63	2093	0.97	5178	1.34
Cleveland, OH	44	11	236	0.52	3488	0.58	2446	1.14	5228	1.35
Los Angeles, CA	48	8	197	0.43	3213	0.53	3046	1.41	5983	1.55
Philadelphia, PA	51	4	278	0.61	3277	0.54	3568	1.66	7389	1.91
Houston, TX	54	6	207	0.45	3052	0.50	3160	1.47	6533	1.69
Paris	64	9	296	0.65	2758	0.46	3482	1.62	5784	1.50
Chicago, IL	65	10	168	0.37	2606	0.43	2861	1.33	5694	1.48
Baltimore, MD	66	7	184	0.40	2572	0.43	2773	1.29	6301	1.63
Munich	67	30	422	0.93	2460	0.41	996	0.46	2176	0.56
San Francisco, CA	77	14	127	0.28	1991	0.33	2114	0.98	4971	1.29
Atlanta, GA	90	16	115	0.25	1610	0.27	1793	0.83	4243	1.10
Kyoto	95	25	229	0.50	1521	0.25	1307	0.61	2415	0.63
Berlin	119	23	238	0.52	1185	0.20	2203	1.02	2859	0.74
Stockholm	158	31	96	0.21	788	0.13	1234	0.57	2166	0.56
Bethesda, MD	176	15	59	0.13	670	0.11	1306	0.61	4373	1.13
Milan	213	26	55	0.12	529	0.09	1438	0.67	2323	0.60
Vienna	216	22	25	0.05	521	0.09	1984	0.92	2903	0.75
Toronto	242	13	49	0.11	454	0.08	2702	1.25	5072	1.31
Oslo	324	59	84	0.18	310	0.05	781	0.36	1335	0.35
Rome	339	28	27	0.06	279	0.05	1736	0.81	2269	0.59
Amsterdam	410	275	36	0.08	219	0.04	57	0.03	223	0.06
Dublin	469	88	34	0.07	183	0.03	619	0.29	958	0.25
Brussels	538	45	18	0.04	155	0.03	1049	0.49	983	0.43
Edinburgh	1096	44	2	0.00	54	0.01	837	0.39	1645	0.43

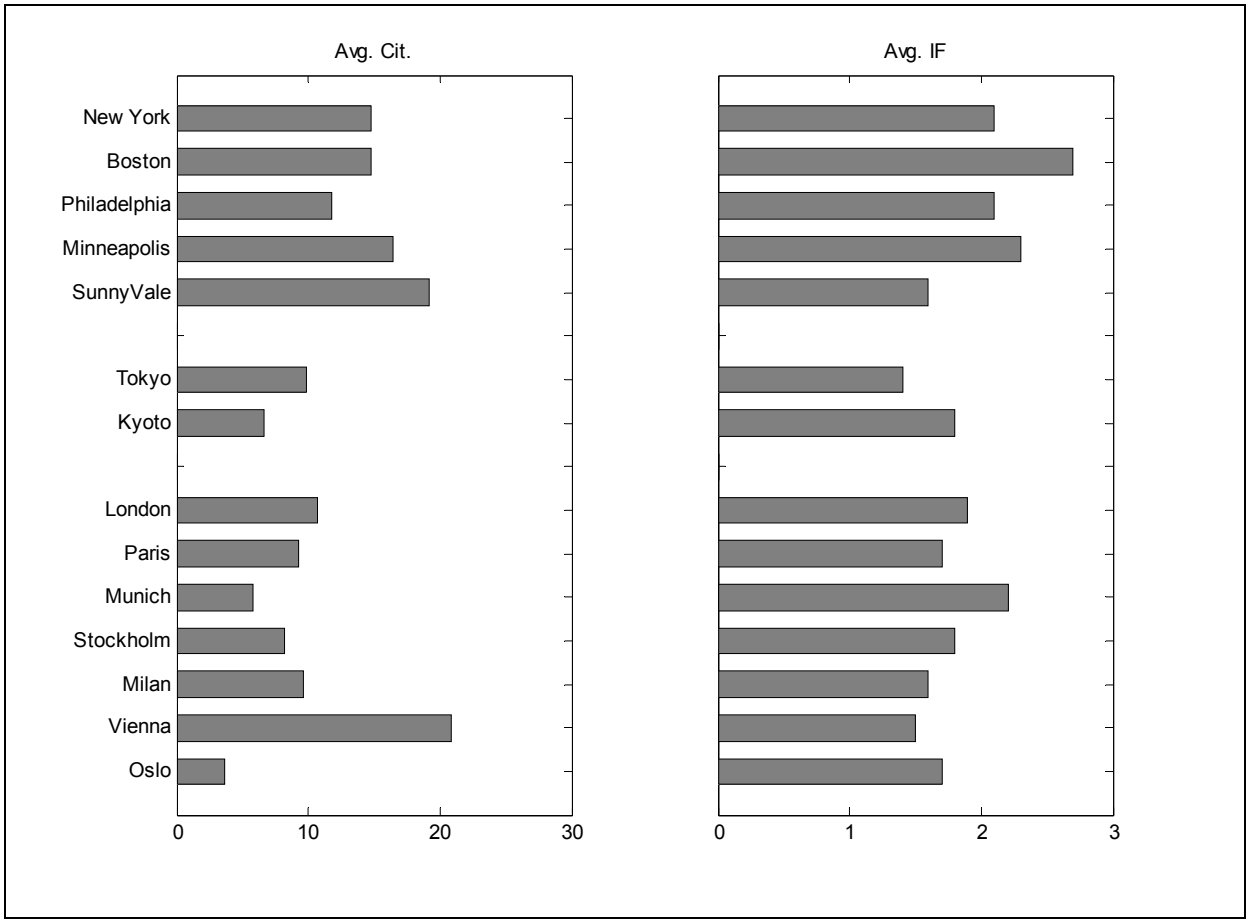
City	Rank Pat.	Rank Publ.	Patents				Publications			
			N	% N	Cit.	% Cit	N	% N	IF	% IF
Barcelona	1209	42	8	0.02	46	0.01	1066	0.50	1660	0.44
Innsbruck	2246	95	9	0.02	14	0.00	468	0.22	475	0.20
Liverpool	2272	94	1	0.00	13	0.00	483	0.22	758	0.20
Madrid	2412	27	6	0.01	11	0.00	1315	0.61	781	0.59

Source: ATA (2004).

Figure 19 reports the average number of citations and the average impact factors of respectively the patents and publications by the cities of the assignee/main author.

The analysis confirms the results of performance on a national level, i.e. the importance of US research with respect to the research in European and Japanese cities.

Figure 19: Average citations and average impact factor, by nationality of assignee/affiliation



Source: ATA (2004).

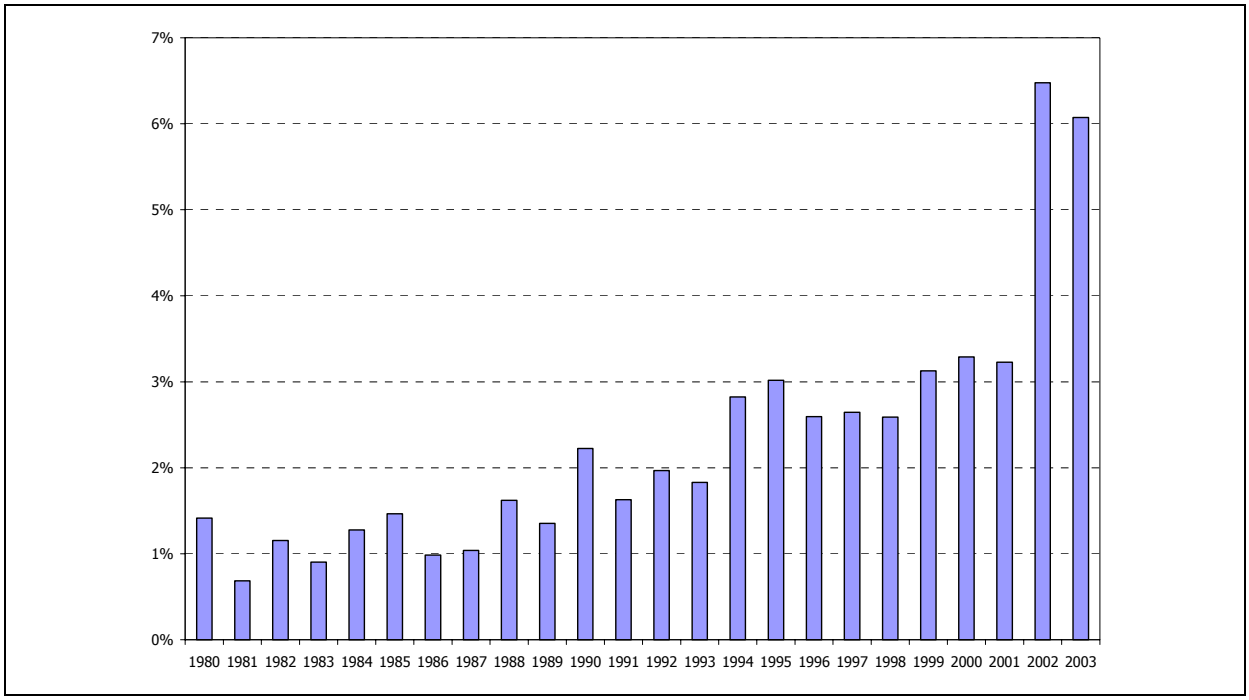
Figure 19 also shows the existence of high heterogeneity within European boundaries and the ranking in terms of publications and of patents, suggesting the existence of different performance of academic and private research. This is true also for US cities. However, the case of Minneapolis is very interesting. This city ranks first in terms of the number of patents,

but it's only 19th when we look at publications. This is due to the fact that this city is the head-quarter of one important medical device firm. However, even though in terms of publications the city is not among the top 15, its research is highly important when we consider the average impact factor of its publications.

On the other side, Sunnyvale is populated by a large number of small firms, and its ranking in terms of publications is very low, also in terms of importance. In Boston, where we have both companies and public research organisations innovating in the medical device field, the "importance" of both patents and publications is very high.

Next, we consider the pattern and characteristics of co-assigned patents, i.e. the patents that are jointly owned by two or more institutions. Patent co-assignment represents a particularly strong form of collaboration among organisations. We considered the US patents with more than one assignee, totalling 13,028 patents.

Figure 20. Share of co-assigned US patents, evolution over time



Source: ATA (2004).

The evolution of the number of co-assigned US patents over the period 1980-2003 is reported in Figure 20. Patent co-assignment in the medical device industry is only a recent phenomenon: the number is very small up to the end of the 80s and increases slightly during the 1990s. We then register a sharp increase in later years from 2001 to 2003. It is interesting to notice that this is concomitant with the decrease in the number of R&D licensing agreements. Whether this is only a transient phenomenon or corresponds to a shift in the way innovative activities are organised within the medical device industry is a question that needs to be further investigated.

Another interesting question is the following: do firms choose collaborators within the same country or is there a cross-national pattern of collaboration among medical device organisations?

Focusing on the patents in the US, we took into account the nationality of each assignee for the patent. Then we considered four broad categories: US, Europe, Japan, and "Others", and analysed the patterns of collaborations among these groups. We only considered the more recent patents, i.e. the patents granted in the years 2002 and 2003.

Table 13. Nationality of partners in co-assigned patents

	US	Europe	Japan	Other
US	563	33	6	28
Europe		102	0	5
Japan			53	1
Other				90

Source: ATA (2004).

The largest number of co-assignment takes place within the US, with almost 70 percent of co-assigned patents involving only US institutions. Moreover, a significant amount of collaborations takes place within European boundaries, and among the patents involving at least one European organisation. About 20 percent also involves a US organisation. Finally, the number of collaborations between Japanese organisations and institutions outside Japan is fairly limited (see Table 13).

The existence of a patent or a publication however does not ensure improvement to health conditions. The impact of new technology occurs at the diffusion stage, where clinicians and government policies influencing the pricing and reimbursement regime of the new device play an important role. Even if a certain health technology is available in a country, its true impact can only be fully realised if there exists adequate dissemination in the healthcare industry (van Merode, Adang, Paulus, 2002).

As a more reliable measure of inventive output, we therefore take into consideration the introduction of medical devices into the US market. Unfortunately, we have no available data about sales of medical device products; therefore, we are not able to assess their diffusion.

Data for the analysis presented here are drawn from the FDA web site[52]. We have extensively checked data sources and have not been able to access similar information for the European countries[53].

European regulation differs from the FDA regulation for marketing devices (Chai, 2000). However, both systems entail different rules according to the potential risk of injury of the new devices present to the users[54] and accordingly assign different regulatory control mechanisms to each class. Moreover, both systems have similar post-market regulatory controls.

[52] http://www.fda.gov/cdrh/consumer/mda/index.html#databases

[53] A European Database on Medical Devices (EUDAMED) is under development. However it will be only accessible to regulatory authorities.

[54] See OTA (1984); http://www.fda.gov/cdrh/manual/ireas.html#24; Eucomed (2004).

In Europe, devices are classified into four categories (Class I, IIa, IIb, and III), according to the risk associated with the device usage, the amount of time that the device is in contact with the human body, and the degree of invasiveness of the device.

A set of essential requirements has been designed to ensure the highest level of patient and user security, besides the device performance. All medical devices must comply with these essential requirements, involving manufacturer registration, and administrative and safety requirements. In addition, all medical devices must comply with a set of conformity assessment procedures, i.e. a scheme designed to regulate the level of scrutiny required to deem a medical technology or device safe, based on the level of its inherent risk to the user, ranging from simple compliance with essential requirements for Class I devices to the Notified Body's evaluation of full quality systems for Class III devices.

If the product conforms to all the applicable community requirements and all the appropriate conformity assessment procedures have been completed, a CE marking is affixed on the product, and the Member States are not allowed to restrict usage of the product, unless evidence of non-compliance of the product is produced.

Following recommendations from FDA classification panels, in the US devices are classified into three regulatory categories:

- Class I contains devices for which general controls are sufficient to provide reasonable assurances of safety and effectiveness (for example: elastic bandages, examination gloves);
- Class II encompasses devices which cannot be classified in Class I, and for which special controls, which might include special labelling requirements, mandatory and voluntary performance standards and post-market surveillance, are required (for example: X-ray devices, infusion pumps);
- Class III applies to devices that cannot be classified in Class I or II and which support life, prevent health impairment, or present a potentially unreasonable risk of illness or injury, like cardiac pacemakers.

Unless exempted[55], manufacturers must register their devices with the FDA. The faster marketing process is the Pre-marketing Notification 510(k), under which the sponsor has to demonstrate that the device to be marketed is substantially equivalent to a legally marketed device that is not subject to PMA, in order to prove safety and efficacy. The notification has to be submitted to FDA at least 90 days before the marketing of the device. If FDA finds that the device is not substantially equivalent to one already in use, then the device must go through a Pre-market Approval (PMA) process[56], which is the most stringent type of device marketing application required by FDA. As a result, the device is also automatically classified into Class III. PMA process requires valid scientific evidence to be provided by the manufacturer in order to prove safety and effectiveness for the device's intended use(s). All clinical evaluations of investigational devices, unless exempt, must have an approved investigational device exemption (IDE) before the study is initiated. This allows the limited use of the investigational device in a clinical study in order to collect safety and effectiveness data required to support a PMA or a 510(k) submission to FDA[57].

[55] Given the low risk involved in their management, most Class I devices are exempted from the Pre-market Notification, while Class II devices usually are not.
[56] Only 1 percent of the medical devices in commercial distribution have gone through the PMA process.
[57] Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)'s require clinical data to support the application.

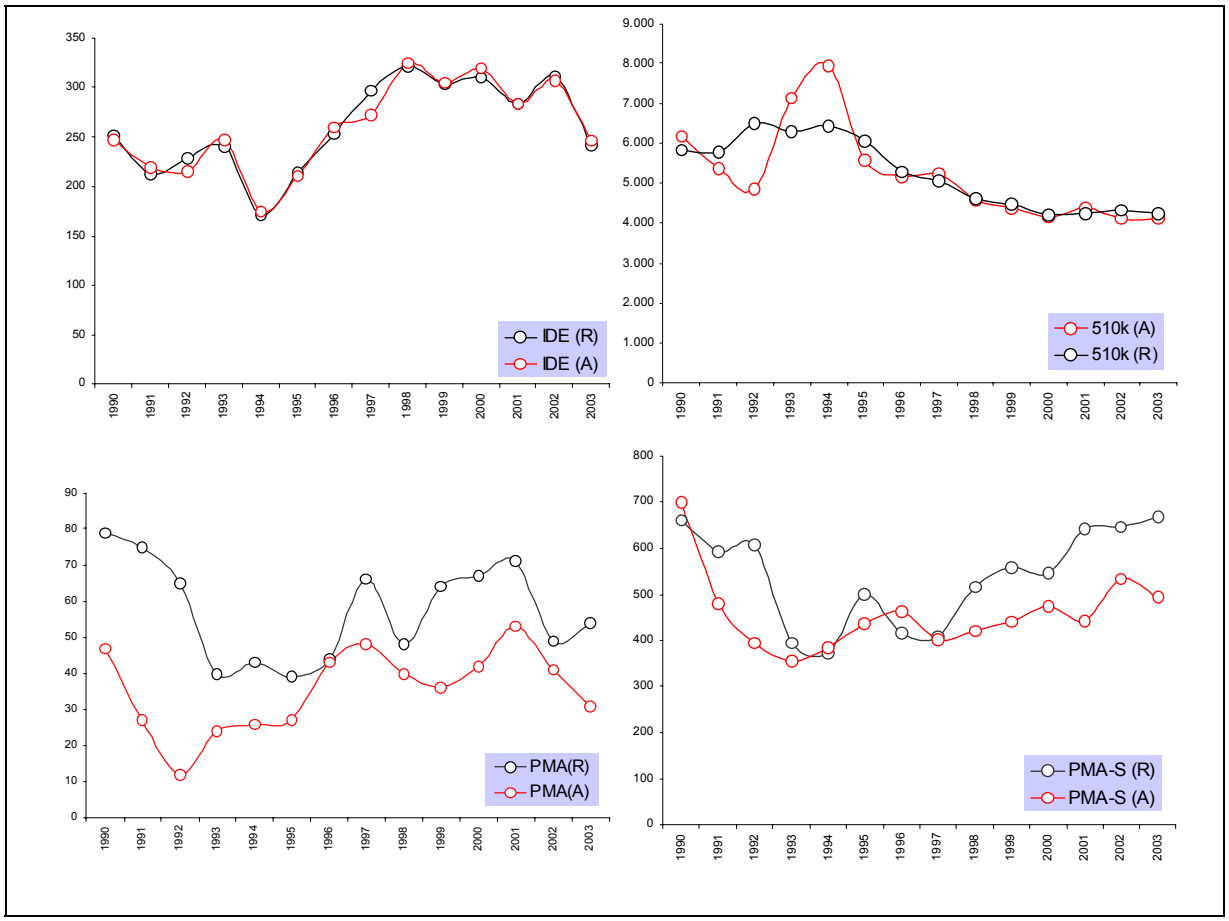
We explored FDA databases containing information about IDE, Pre-marketing Notifications, and PMA.

Figure 21 reports the evolution over time of IDE, 510(k), PMA, and PMA supplements distinguishing between the time of request (R) and of approval (A).

The number of IDE has increased sharply from 1994 to 1998, and it is declining in the later years. The number of Pre-marketing Notifications, after a slight increase in the early 1990s, is decreasing over time, and it is been almost constant in the latest years. No clear trend emerges when we look at the number of PMA and PMA supplements.

Notice the lower figures involved when dealing with PMA as compared to 510(k) notifications: the number of devices requiring clinical trials are a small percentage of the total number of devices in the market. Most devices are classified into the lower risk category.

Figure 21. Evolution over time: PMA, PMA-S, IDE, 510(k)



Source: Our elaborations on FDA (2004a; 2004b).

Table 14 reports the share of devices by class, classified according to their level of risk.
We considered all the medical devices in commercial distribution in the US by both domestic and foreign manufacturers with a known owing corporation.

Table 14. Share of device by class

Country of corporation	Number of products	Share by Device Class (%)			
		Unclassified	Class 1	Class 2	Class 3
US	265,078	2.33	45.82	48.58	3.27
EU15	25,802	1.95	57.67	39.00	1.38
NMS	219	0.46	76.71	22.37	0.46
EU25	26,021	1.94	57.83	38.86	1.37
Japan	3,713	1.45	38.81	58.69	1.05
Germany	11,885	1.85	67.57	29.78	0.80
UK	4,105	2.90	42.05	53.69	1.36
France	2,532	2.09	57.98	37.20	2.73
Sweden	2,223	1.71	43.95	52.27	2.07
Denmark	2,073	1.50	48.91	48.09	1.50
Switzerland	1,678	1.97	66.09	31.53	0.42
Canada	1,381	4.13	59.23	35.41	1.23
Italy	1,359	1.40	63.28	33.55	1.77
Ireland	592	0.00	37.16	59.12	3.72
Belgium	391	0.00	60.10	39.39	0.51
Netherlands	265	4.53	50.19	43.77	1.51
Spain	157	1.91	57.32	39.49	1.27
Poland	110	0.91	80.91	18.18	0.00
Austria	106	1.89	66.98	27.36	3.77
Finland	106	5.66	47.17	47.17	0.00
Norway	89	5.62	38.20	56.18	0.00
Iceland	63	0.00	82.54	17.46	0.00
Czech Republic	48	0.00	85.42	12.50	2.08
Hungary	39	0.00	58.97	41.03	0.00
Lithuania	16	0.00	81.25	18.75	0.00
Total	*316,674*	*2.28*	*48.93*	*45.90*	*2.90*

Source: our elaborations on FDA (2004d).

Even though it is problematic to compare the number of products commercialised by US and European corporations, interesting information can be drawn from the table. Germany is the European country with the largest presence in the US with 11,885 products, followed by the UK with 4,105 products. Japan ranks only third with 3,173.

Also, it is interesting to compare the share of devices classified in Class I, II, and III, identifying devices with a different level of potential risk for human health, and, due to the fact that they require closer inspection by the relevant authorities, with different levels of investments and complementary assets.

The share of Class I (low risk devices) is higher than 80 percent, pointing to an industry focused on low risk devices, in Poland, Czech Republic, Iceland and Switzerland.
Austria and Ireland are the European countries with the largest share of products classified into Class III, the class with higher-risk devices requiring clinical trials.
The result for Ireland is interesting when coupled with the large ownership of US-based corporations of Irish manufacturers (see Table 7 in Section 6).
In fact, a large share of firms in the manufacturing sector in Ireland is owned by foreign corporations (see Barba Navaretti and Venables, 2004). Nowadays almost 50 percent of the Irish manufacturing employment is in foreign-owned firms (61 percent of them being US firms), as compared to an average for the other European countries (EU-15) of 19 percent. Despite this general pattern, medical and optical equipment are among the sectors where foreign industry predominates.
Various factors have contributed to the strong increase in FDI inflows in Ireland.
Starting from the late 1950s, the country introduced a zero tax rating on profits derived from manufactured exports, making Ireland a preferred exports platform for firms in Continental Europe and the US. By the 1980s, Ireland had become a well-established European production base for US multinationals, therefore being well positioned to capture the FDI inflows when US corporate strategy began to respond to the forthcoming Single European Market in the late 1980s-early 1990s.
Besides the tax regime, other factors are likely to have been of importance.
First of all, the role played by Ireland's Industrial Development Agency (IDA), that was able to identify the sectors most suited for Ireland's development aims, and that had an influence on successfully upgrading the human capital and physical infrastructure required to attract firms from these sectors.
Moreover, the labour market conditions, the quality of public infrastructure (also enhanced by IDA), and the efficiency of the public administration system have also likely been of importance.

7. STATISTICAL SHORTCOMINGS FOR THE SECTOR: ANALYSIS AND PROPOSALS

Summary of the chapter

The lack of systematic effort at an international level to collect, integrate, update and diffuse primary data and information on the state and the evolution of the medical device industry represents a severe limitation to this study and to previous analytical efforts. This also dramatically reduces the possibility of formulating any reliable policy action to enhance the competitiveness and productivity of the EU medical device industry, limit the effect of market failures in healthcare systems and design and support the constitution of a European system of innovation.

After describing the main characteristics and shortcomings of the data sources employed in the analysis, we propose a statistics framework for the creation of a data collection system targeted at the medical device industry.

Firstly, single national statistical offices, regulatory authorities and international institutions urge the identification of a common definition for the medical device industry and a classification of relevant medical device sub-sectors based on both market and technological factors.

Secondly, regulatory authorities and public institutions in general should provide incentives to private companies to communicate micro-level data on their activity.

Thirdly, no efficient political action to support the competitiveness of the industry in Europe should be designed without the possibility to control the actual state of the industry and the effect of public intervention.

Data and statistical information are the unique base upon which informed policy actions can be undertaken.

7.1 Description of data sources

Data used in this Study have been extracted by different sources. Both at the macro level, and even more so at the micro level, comparability of the figures across countries and sub-sectors is severely limited by non-homogeneous definitions and classifications employed by the different data sources.

The analysis at the country level has been carried out regardless of the origin of the company and considering the medical device industry as a whole. The data for the analysis of the medical device industry competitiveness and innovativeness have been drawn from public sources, namely the Eurostat, the Japanese Ministry of Health, Labour and Welfare, and the data supplied by the US Census Bureau, briefly described in the following. In addition, market data for selected sub-markets have been obtained through Industry Trade Associations.

For the European countries, data have been collected from the NewCronos database (Eurostat, 2004a; 2004b). We considered the NACE 33.1, which reports data on “Manufacture of medical and surgical equipment and orthopaedic appliances”.

The data cover the period 1995-2002 and include[58]:

- manufacture of instruments and appliances used for medical, surgical, dental or veterinary purposes (electro-diagnostic apparatus such as electrocardiographs, ultrasonic diagnostic equipment, scintillation scanners, nuclear magnetic resonance apparatus, dental drill engines, sterilisers, ophthalmic instruments);
- manufacture of syringes, needles used in medicine, mirrors, reflectors, endoscopes, etc.;
- manufacture of apparatus based on the use of X-rays or alpha, beta or gamma radiation, whether or not for use in human or animal medicine (X-ray tubes, high-tension generators, control panels, desks, screens, etc);
- manufacture of medical, surgical, dental or veterinary furniture (operating tables, hospital beds with mechanical fittings, dentists' chairs);
- manufacture of mechano-therapy appliances, massage apparatus, psychological testing apparatus, ozone therapy, oxygen therapy, artificial respiration apparatus, gas masks, etc.;
- manufacture of orthopaedic appliances (crutches, surgical belts and trusses, splints, artificial teeth, artificial limbs and other artificial parts of the body, hearing aids, pacemakers, etc.).

A major limitation of the NACE classification is the exclusion from the medical device aggregate of the high-tech chemical and biochemical-based devices such as in vitro diagnostics (that are classified under "chemicals") and medical-impregnated products such as gauzes and bandages (that are grouped under "pharmaceutical preparations"). As a result, estimates of the R&D intensity of the sector for the European countries are biased downwards.

Data for Japan are based on data published by the Ministry of Health, Labour and Welfare (MHLW), and they have been obtained through the Japanese Federation of Medical Device Associations (JFMDA). Data about the composition of the industry and R&D employment and expenditures are based on the results of a survey of a subset of the firms that are active in the industry. The data are likely to reflect the characteristics of the larger firms, since smaller firms are less likely to respond to the survey, due to the lack of personal resources. Unfortunately, it is not possible to assess the response rate on the basis of the firm size, since we do not have prior knowledge about the composition of the industry.

For the US, we have not been able to find data related to the medical device industry as a whole. We therefore accessed different data sources, including data published by the US Census Bureau, and summed up the data of the following NAICS sector:

- 325413: In-Vitro Diagnostic Substance Manufacturing;
- 339111: Laboratory Apparatus and Furniture Manufacturing;
- 339112: Surgical and Medical Instrument Manufacturing;
- 339113: Surgical Appliance and Supplies Manufacturing;
- 339114: Dental Equipment and Supplies Manufacturing;
- 339115: Ophthalmic Goods Manufacturing;

[58] A detailed description of the class is available through the European Commission web site http://europa.eu.int/. Data contain many missing value, therefore the computation of the European aggregates (both EU-15 and EU-25) is problematic, especially for the R&D data.

- 334510: Electromedical and Electrotherapeutic Apparatus Manufacturing;
- 334517: Irradiation Apparatus Manufacturing.

The analysis was based on various measures aimed at assessing the capabilities and competitiveness of European industry, especially in comparison with the US and Japan.

As for the analysis at the sub-market level, we considered data from a proprietary database, Compustat North America (Standard and Poor's Compustat®, 2004b), which reports data about public companies in the US and Canada. In this analysis larger firms are over-represented. In addition, Compustat assigns each firm to a specific industry on the basis of its principal line of activity; therefore, it is not possible to distinguish the portion of R&D (and sales) that directly relate to the medical device industry for the large and diversified multinational companies.

Data on international trade flows usually report information at the product level, allowing us to also perform analysis that considered well-defined product classes.

Data have been extracted by two different sources: the Eurostat ComExt Database and the Trade Database of the US International Trade Commission. The data sources respectively classify imports and exports of European countries and the US, according to the sources and destinations of international flows.

As for the classification of products, the two data sources employ two different systems for grouping the devices: the European data employs the Combined Nomenclature (CN), while the US International Trade Commission database is based upon the Harmonised Tariff Schedule (HTS). However, there exists full agreement between the two classification systems at six-digit level, i.e. the level of aggregation that we employ in the analysis.

In order to be consistent with the analysis presented at the country level, we decided to resemble products by manufacturers classified in the NACE 33.1. Particularly, we considered the following classes (at the four-digit level):

- **9018**: instruments and appliances used in medical, surgical, dental or veterinary sciences, including scintigraphic apparatus, other electro-medical apparatus and sight-testing instruments n.e.s.;
- **9019**: mechano-therapy appliances; massage apparatus; psychological aptitude-testing apparatus; ozone therapy, oxygen therapy, aerosol therapy, artificial respiration or other therapeutic respiration apparatus;
- **9021**: orthopaedic appliances, including crutches, surgical belts and trusses; splints and other fracture appliances; artificial parts of the body; hearing aids and other appliances which are worn or carried, or implanted in the body, to compensate for a defect or disability;
- **9022**: apparatus based on the use of x-rays or of alpha, beta, or gamma radiation, whether or not for medical, surgical, dental or veterinary uses, including radiography or radiotherapy apparatus, x-ray tubes and x-ray generators, high-tension generators, control panels and desks, screens, examination or treatment tables;
- **9402**: medical, surgical, dental or veterinary furniture, e.g. operating tables, examination tables, hospital beds with mechanical fittings and dentists' chairs; barbers' chairs and similar chairs having rotating as well as both reclining and elevating movement.

At the micro-level, different sources have been considered to provide a comprehensive picture of the innovation process in medical devices. Most of the analysis is based upon the ATAdb

(ATA, 2004) providing detailed information, at the firm level, about various aspects of the innovation process in medical devices. In particular, we considered patents, publications, and deals among firms in the medical device industry. As for product introduction, we have been forced to use data about the US market, freely available on the FDA web site. We are not aware of data about the introduction of medical devices in Europe that are suited for statistical analysis. Patents and publications would be also available through public web sites, but in a form that needs processing before being suited for statistical purposes.

Unfortunately, the comparison of the indicators devised for the description of the innovation process in different sub-markets is complicated by the different classification employed by each piece of information. Patent data employ a technology-based classification, which is different and not easily reconciled with the classification employed for publications and product introduction.

The first step towards the development of a comprehensive statistical system for the analysis of the medical device industry a national level is certainly a clear definition of the industry and of the sub-markets involved.

A definition is given in the European Union Medical Devices Directive (93/42/ECC), article 1, which covers "*any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:*

- *diagnosis, prevention, monitoring, treatment or alleviation of disease;*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;*
- *investigation, replacement or modification of the anatomy or of a physiological process;*
- *control of conception;*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

Against this background, the Directive has provided a common background for regulatory framework for market access, international trade relations and regulatory convergence of the industry. This is not yet reflected in the definitions and classifications in the data.

In our Study, we have been forced to adopt broader or narrower definitions of medical devices, in order to address specific issues or, for the empirical analysis, to account for data availability.

In addition, since the medical device industry is highly heterogeneous, a detailed classification of the industry is needed in order to compare sub-markets at the country level.

Besides under-representing the high-tech part of the industry, the NACE classification does not allow to recover fine-grained information at the sub-market level, in order to assess the competitiveness of European countries in different sub-sectors. The current revision of the NACE classification should consider the provision of statistics at the sub-market level and should set a harmonised definition of these sub-markets across different countries. An effort should be made in order to isolate the in-vitro diagnostic industry from chemicals and pharmaceutical preparations, as to include this segment into the medical device aggregate statistics at the European level.

7.2 Towards a statistics framework for medical devices

The definition of medical devices set forth in the Global Medical Device Nomenclature (GMDN) might be adopted for data collection purposes. The definition has been devised by the Global Harmonisation Task Force (GHTF), founded in 1993 by the governments and industry representatives of Australia, Canada, Japan, the European Union and the United States to encourage a convergence in standards and regulatory practices related to the safety, performance, and quality of medical devices (WHO, 2003).

The GHTF has proposed the following definition of medical devices:

"Medical device" means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury
- investigation, replacement, modification, or support of the anatomy or of a physiological process
- supporting or sustaining life
- control of conception
- disinfection of medical devices
- providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body and which does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

We would therefore recommend the Commission to support the creation of a statistical data collection system targeted at the medical device industry as defined above. The importance of the industry in supporting health improvements and in increasing the quality of life is uncontroversial. However, informed policy actions can be only undertaken on the basis of data and statistical information.

Against this background, we take on some of the issues identified in the *Biotechnology Statistics Framework* (OECD, 2001, 2004) and we try to set up a statistic framework for the medical device industry.

We have identified a set of key indicators that are useful for describing various features of the industry and matched each indicator with a type of policy, trying to evaluate the usefulness of each indicator for different policy options.

The results are summarised in Table 1 (adapted from Arundel 2003; OECD, 2004), where we also indicate the availability of data for the construction of the selected indicators among the EU-25 countries. Indicators with a "high" rating are available for 15 or more European countries, those with a "medium" rating are available for four to 15 countries, and those with a "low" rating are available for three or fewer countries.

The last column of Table 1 provides information on the source of the original data for each indicator. Four main types of organisations collect data: government or international public organisations (GOV) such as the USPTO or EPO, national statistical offices (NSO),

academics, usually based at universities or semi-independent public research organisations (ACD), and private organisations, such as consultants or industry trade groups (PRI).

In some cases, the indicator is collected by more than one type of organisation. If this is the case, the type of organisation providing more accurate data is listed first.

We have tried to evaluate the usefulness of each indicator in terms of policy options. In particular, the indicators are divided into three main fields including those for (adapted from OECD, 2001, 2004; Arundel, 2003):

1. The development of the medical device industry, which can be further classified into: (a) supporting research in medical devices; (b) fostering the diffusion of knowledge and expertise among different actors; (c) supporting the commercialisation of medical devices.
2. The economic impacts and social issues, including the impact of medical devices on health, not directly relevant to a specific set of policies, but rather of vital importance and applicable to every policy areas.
3. Industrial policy: a detailed description of the main feature of the industry is the necessary ground for guiding any policy aimed at fostering the competitiveness of the European medical device industry.

Table 1. Medical device indicators: relevance for main policy areas

Indicator	Supporting research	Dissemination of knowledge	Commercialisation and diffusion	Impact and benefits	Industrial policy	Availability by country	Main data source
Patents granted	✓	✓		?		High	GOV/PRI
Patent share of worldwide patents	✓	✓		?		High	GOV/PRI
Patent growth rate	✓	✓		?		High	GOV/PRI
Patent applications	✓	✓		?		High	GOV/PRI
Scientific literature and impact	✓	✓		?		High	GOV/PRI
International trade			✓			High	GOV
Total R&D expenditures	✓				✓	Medium	NSO
Production					✓	Medium	NSO/PRI
Value added					✓	Medium	NSO/PRI
Number of employees					✓	Medium	NSO/PRI
Number of firms			?		✓	Medium	NSO
Number of MD firms by size class			?		✓	Medium	NSO/PRI
Number of MD firms by area/field			?		✓	--	???
MD alliances		✓	?			Medium	PRI
MD M&A		✓	?		✓	Medium	PRI
Technology licensing		✓	?			Medium	PRI
Public R&D funding	✓			?		Low	NSO
Private R&D funding	✓			?		Low	NSO
Funding sources for SMEs	✓			?		--	NSO/GOV
MD revenues/sales					✓	Low	PRI
Market approval for MD			✓		✓	--	GOV
Co-patenting or co-publishing		✓		?		Low	PRI/ACD

As the medical device industry is highly research intensive, we first considered the information necessary for supporting research within this sector. There are two main ways in which government can support research: direct research activities by the public sector and direct and indirect government funding of the private sector research. Moreover, the public sector can sustain the private sector direct investment in medical device innovation by establishing a stable environment with respect to reimbursement, funding, and price mechanisms.

Relevant indicators for the public funding of research for medical devices consist of both basic data on public R&D spending in medical devices and intermediate output measures of public research activities such as patenting by public research institutes. The availability of data about the sources of funding for the private R&D activity is limited within the medical device industry, and also we know very little about the funding sources for small and medium enterprises.

Patents and scientific literature can be useful sources of information. Actually, these indicators have little or no direct relevance to the design of specific policies, but they provide useful insights into national capabilities. However, they can help governments decide if they need to introduce a range of policies to promote national capabilities in medical devices, and they can be employed as an output measure of the success of government actions undertaken to promote research in the field.

An effort needs to be undertaken to classify patent information into public and private sources. In addition, academics are often involved in the research undertaken by large firms, but the public research organisation is not mentioned among the assignee(s) in the patent document.

Another relevant aspect of patents and of the scientific literature is their contribution to the diffusion of knowledge within the industry. Many public policies provide incentives for collaboration in order to diffuse knowledge and expertise among different actors. These include subsidies to private firms to contract research out to public institutes, passive incentives to increase the number of contacts between public research and private firms, and research subsidies for private firms that require collaborative networks. Under this perspective, it is of interest to analyse the magnitude and direction of M&A and alliances, and of technology licensing. Moreover, data about co-patenting and co-licensing are useful sources of information for understanding the patterns of knowledge diffusion within the sector. Under this perspective, and given their different incentives for doing research, it is of interest to characterise the University-Industry linkage (if any) by analysing the patterns of co-patenting and co-publishing of private firms and public research organisations.

A major limitation to the analysis of the medical device sector is the lack of detailed and comparable data on the state and evolution of products, firms, industries and markets. A first important step to partially overcome this problem at the EU level would be the completion of the European Database on Medical Devices (EUDAMED). EUDAMED is under development with the aim of helping European authorities to conduct market surveillance on medical devices through information exchange[59]. Since the first pilot study launched in 1997, some progress has been made; however, EUDAMED is not yet operational. In particular, the decision to use a common notification by National authorities and the adoption of the Global Medical Devices Nomenclature (GMDN) constitute two important steps toward the implementation of a European Database for medical devices.

EUDAMED will be an information system for exchanging legal information between national competent Authorities and the Commission. Only these entities will have access to the database. Nevertheless, the "EUDAMED Global Implementation Plan" states that "a more widespread access to the system may be allowed following discussion, at a later stage". Given the nature of the data that will be loaded in the database, we strongly recommend a wider access to the database, also for the purpose of statistical analysis.

[59] Information about EUDAMED has been obtained at http://europa.eu.int/idabc/en/document/2256/16#what.

High quality operational data will be loaded in the database as specified in the medical devices Directives. These will include:

- data related to registry of manufacturers, authorised representatives and devices;
- data related to certificates issued, modified, supplemented, suspended, withdrawn or refused according to established procedures;
- data obtained in accordance with the vigilance procedure on incidents or near-incidents which occur during the use of the medical device.

Besides regulatory benefits, in terms of registration, vigilance and other investigations to the relevant national authorities, the availability of information about manufacturers and their products at a centralised place will greatly enhance the possibility of statistical analysis of the industry, allowing a deeper understanding of the characteristics of the medical device industry in Europe, and opening up the possibility for the suggestion of targeted policy actions.

At a later stage, further information might be required from the companies, including product sales, R&D expenditures, patent applications, deal activities, in order to provide a database that is suited for the analysis of competitiveness and innovativeness of the medical device industry in Europe. This as a prerequisite for the suggestion of policies aimed at enhancing the competitiveness and innovativeness of the European medical device industry.

8. POLICY RECOMMENDATIONS

This chapter proposes strategic recommendations to the European Commission and Member States on policy options for the medical devices sector, based on the analysis of previous chapters. As a starting point, policymakers must be aware of the inherent complexities of the medical device sector, whereby a heterogeneous and vital innovative medical devices industry is also a crucial component of European healthcare systems. This means that no easy-menu exists for policies aimed at controlling costs while enhancing the quality of health services, as well as innovation and competitiveness of the European medical device sector. The endorsement of these distinct objectives implies trade-offs and difficult resource allocation decisions.

The following policy recommendations are based on another general principle: policy options need to rely mainly upon market incentives, rather than on administrative mechanisms of control. Generally speaking, administrative regulation applied to the markets for health services and products, as well as to other markets, has often proved distorsive, detrimental for innovation, and ineffective in the long-run. Commonly addressed options such as limiting the supply of medical technology, constraining investments in med-tech R&D and imposing administrative caps on the supply side of the market cannot be considered as viable options for Europe in the long-run. All the following policy options are directed at enhancing market signals and incentives in a coherent framework, and at lowering the adversity of the trade-offs by leveraging on the overall efficiency of the system.

1. Member States and the European Commission should clearly state the key policy objectives and address the policy options in their full complexity and trade-offs

The Study has revealed the existence of a common constraint – i.e. expenditure control – to three key policy objectives that are high on the agenda of the European Commission and all Member States: quality of health treatment, innovation and competitiveness of the medical device industry.

As seen in the Study, the debate and literature on innovation in medical devices and technological progress in medicine has sometimes confounded the notions of quality and innovation. Innovation for instance has often been misconceived as a synonymous of improvement in medical practice. The Study has also assessed and highlighted that these objectives are of top-relevance for all European and Western countries, and are no longer deferrable. Governments need to take political choices on how to face the tension between their commitments to quality of care, medical innovation, and healthcare cost-containment needs. Nonetheless, for the most part, policies have been unwilling to acknowledge the inherent trade-offs between healthcare costs, people's access to high quality care, and innovation.

A preliminary exploration of the viable options and a better understanding of the interdependencies among policy objectives are strongly recommended. This prerequisite is vital to the development of coherent policy agendas and to the diffusion of consistent signals to the actors in the medical device sector.

2. Member States should enhance their coordination to define concerted policies in order to send consistent signals to the market, reduce uncertainty, orient R&D and innovation toward cost-reducing or affordable technologies

Both the theoretical and empirical analyses presented in the Study have shown that the diffusion of a number of existing technologies has been highly responsive to market signals and insurance-related incentives. Decisions affecting the use of, and payments for, treatments based on medical

devices affect the expectations about profitability of various prospective products and the incentives to develop and produce them. In the past, the incentives injected in the market favoured the development of new medical technologies, regardless of their costs. The change in the incentives, marked by the move toward prospective-based insurance systems, altered the direction of medical innovation in favour of the development of cost-reducing and efficiency-enhancing medical devices and practices.

Measures that affect the incentives to innovation, such as payment and reimbursement schemes, have proved to be policy tools for cost-conscious health insurers, capable of directing R&D incentives and innovation toward more "favourable" trajectories. Given the fact that medical device manufacturers operate under shorter R&D time horizons than, for instance, pharmaceutical manufacturers, the time for action of these incentives is of mid-to-short term.

In order to turn this mechanism into an effective policy option, it is necessary that a) these incentives are operated consistently by a large "critical" mass of health schemes/systems; and b) a reference criteria for "efficiency-enhancing" is set and shared through technology assessment tools, since the key issue for health systems is not only how much costs are rising but also what is being achieved in terms of health benefits for the resources consumed (Recommendation 3).

Medical R&D incentives are at present determined by the uncoordinated decisions of governments and private-sector insurers in each nation. The ambiguity of public policy on the issue of medical devices and healthcare cost-containment is generating economic uncertainty in the R&D environment. This is adding new uncertainties to the process by which innovator companies bring new products to the markets, to the detriment of the innovative process.

Democratic societies find it difficult to resist incurring the costs of providing widespread access to new technologies and medical advances, regardless of their costs. A coordinated agenda for the Member States for the sector – oriented at maintaining the rate of innovation, but redirecting it toward cost-reducing technical change – could influence the multitude of new medical devices in their R&D investment decisions, rather than making the hard choices on utilisation only after products have been developed.

3. Members States should enhance the use of evidence-based medicine and health technology assessment (HTA) analysis as an input to: a) their coverage policies; b) to their policies aimed at incentivating and strengthening research, development, and innovation in medical devices

The policy trade-offs inherent to the medical device sector should be translated to a long-term cost-effective equilibrium. Greater adherence to the practice of evidence-based medicine and greater assessment of technology before and once in use may all lead to gains in efficiency.

The recognition that healthcare technology contributes to health spending growth has led to a recent expansion of the technology assessment focus, from "Is it safe?" and "Does it work?" to include considerations of cost-effectiveness, thus becoming "Is it worth it?". This would move the present debate from how much costs are rising due to innovation in medical devices to what is being achieved in terms of health benefits for the resources consumed. Conducing cost-effectiveness analysis will not remove the need for difficult resource allocation decisions. But explicitly illuminating the trade-offs involved should help the process.

Implementing an economic criterion will also create an incentive for producers to develop cost-effective products in the first place (Recommendation 2).

Despite the fact that the number of well-designed clinical trials have grown dramatically in the past few years, and that medical journals now routinely publish cost-effectiveness analysis, the use of

HTA by policymakers as an explicit part of the decisions on coverage, funding and clinical guidance, though increasing, is still limited, and confined to a minority of Member States.

This Study recommends to all Member States the use of HTA methodologies as an input to rational choices. An extensive use of this tool would not only contribute to the efficiency of the national choices, but also to the broader system of consistent signals to the industry (Recommendation 2).

Since the health impact of the devices cannot be isolated by the system where it is used the responsibilities for conducting HTA should stay at the level of a set of "centers of excellence" under the responsibility of Member States. The European Commission should favour the diffusion of information about medical technology innovations and best medical practices throughout Europe.

Unlike the pharmaceutical sector, where new products go through a costly series of regulatory clinical trials during development and pre-launch, HTA applied to medical devices should be performed mainly at the post-market phase, due to: a) the fact that once a class of devices is established with accepted clinical data, pre-market clinical trials for incrementally improved devices are not required for CE Marking, so no clinical data is available for pre-marketing; b) many device-based interventions are subject to a learning curve which improves outcomes after marketing; c) incremental post-launch product improvements d) the dependence of outcomes from system factors, that cannot be assessed *a priori*.

HTA of medical devices can be seen and used not only to illuminate cost-containment decisions, but also to wise up industrial policy and promote innovation. Long-term evaluation of the benefits and costs (clinical, social, economic and system-wide) of a technology in a given system provides the "value" of the technology and of the innovation that introduced it into practice.

The economic and medical evidence provided by HTA can therefore be used to set up innovation-oriented pricing and reimbursement schemes.

In this perspective HTA and the long-term evaluation of the benefits and costs are instruments to:

- appreciate the application spectrum of innovative outcomes;
- promote the uptake of valuable medical innovations;
- ensure rapid and equal access to new medical devices and best practice throughout Europe;
- provide incentives to innovative ventures;
- promote the collaboration among institutions in order to identify unmet clinical needs.

4. The Commission should reinvigorate the process of coordination and harmonisation of national HTA processes and experiences

The process of implementation of HTA is at present progressing, with Member States adopting different metodologies and standards. Exchangeability and access to the evidence-based information for policy-making and practice obtained through HTA would instead be enhanced by the harmonisation of the methodologies and standards of data compilation. The processes and initiatives in place (the ECHTA/ECAHI project) have so far led to partial results.

The Commission should reinvigorate this process of coordination through the enhancement and sponsorship of an effective and well-endorsed "European Network for Medical Technology Assessment". The mission of the network should include the development of agreed harmonised EU standards for HTA in medical technologies, together with the collection and dissemination of the knowledge produced all along the diverse pipelines of R&D for medical devices: individual scientists, physicians, academic medical centers, small device companies and multinational corporations.

The objective of the network would be to assist the European Union, its Member States and the candidate countries to plan, deliver and monitor health services effectively. The network should involve those working actively on assessments in healthcare throughout the Europe Union, focusing on those in the public sector, but welcoming those working in other settings. The network should work closely with global collaborative efforts in the field, such as INAHTA (The International Network of Agencies for Health Technology Assessment) and the US Agency for Healthcare Research and Quality under the Department of Health and Social Services. As the Agency of Healthcare Research and Quality in the US and the INAHTA, the network will focus on the key technologies identifitied based on mission-oriented programmes.

5. Member States should diversify the financial structure of medical expenditure as a mean to ease the policy trade-offs and to achieve financial and social sustainability

Considerations in the Study suggest that the debate on the impact and sustainability of medical devices expenditures needs to be enriched in order to include elements related to social expenditure composition and overall sustainability. Projection of health and social expenditure for EU countries suggests in fact that, independently from the technological innovation in medicine and medical devices, EU Members will be asked to adopt significant reforms of their social security systems, in order to ensure their financial and social sustainability.

To this regard, international experience as well as economic considerations on the efficiency of the financial structure of social expenditure, suggest the existence of benefits associated to a higher heterogeneity of the financial sources, through an increased role for private insurance-based funds (health funds, when applied to the health sector), the so-called “private institutional pillar”. Diversification should preserve the fundamental goals of the social system and, at the same time, enhance the efficiency of the healthcare system.

The scenario, for the medical device sector would be among other things, a partial loosening of budget constraints as well as the focus on cost-containment. This would allow more room for high performance products both in the public and private markets.

6. Member States and the European Commission should promote and establish a coherent statistical framework for the analysis of the competitiveness and innovativeness of the medical device sector in Europe

The Study has revealed the inadequacy of the available statistical framework for the analysis of the medical device sector, both at the aggregate and at the disaggregate levels.

The present lack of a systematic effort at the international level to collect, integrate, update and diffuse primary data and information on the state and the evolution of the medical device industry severely constrains the possibility to formulate reliable policy actions to enhance the competitiveness and innovativeness of the EU medical device industry. Moreover, data availability is a prerequisite to design and support the constitution of a unified European system of innovation.

The first step toward the design of a statistical framework for the analysis of the medical device sector is the adoption of a common definition of the industry, agreed and accepted by all the actors involved in the data collection process such as the definition set forth by the Global Healthcare Unification Task Force. In addition, given the heterogeneity of the medical device sector, that is composed of a wide range of different products, the identification and adoption of a unified classification system at the international level is needed.

In Chapter 6, we have proposed a set of indicators, that can illuminate policy decisions, and on which statistical collection should focus. Among these are data on the number of patents and

publications; on the introduction of new products in the marketplace; on the number, size and dynamics (birth and deceases) of companies, and on their R&D expenditures, sales, value added, number of employees, and collaborative ventures.

Data gathering and management should be centralised at Eurostat.

Appropriate market-based incentives should be devised to enhance: i) the transparency of the administrative procedure for determining the value of medical devices, ii) the transparency of the decision-making process for the review of new and existing procedures and technologies and iii) the participation of companies, hospitals, as well as local and national institutions in the provision and diffusion of medical data and information on the sector. This issue is linked with the recommendation of undertaking systematic assessments of the value and degree of innovativeness of medical devices on the market. The design of market mechanisms based on innovation-oriented premium price schemes will provide incentives for investments in R&D and for the disclosure of unbiased data and information. Data collected this way could then be used to inform, design and monitor policy choices and trade-offs (see Recommendation 1) and initiatives for the promotion and the support of competitiveness and innovation.

Market-based incentives and HTA can provide incentives to companies and public institutions for a transparent and unbiased provision of information and data on the value of their innovation, on their innovative efforts as well as on market dynamics. Such information and data can be of use only through a systematic and unified statistical framework, that needs further development as the analysis has revealed. The establishment of a unified and leading European system of innovation in medical technologies need to be well-informed and supported by data at all stages of action.

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ANNEXES

ANNEX TO CHAPTER 4

Table A.4.1. DALY – disability adjusted lost year (x *100*) by age, sex and cause, 2001 worldwide

		0–4	5–14	15–29	30–44	45–59	60–69	70–79	80+	Total
Male	***Cardiovascular diseases***	*3,542,736.14*	*1,760,964.89*	*6,943,255.86*	*16,417,432.57*	*40,595,419.76*	*36,278,481.76*	*27,775,327.79*	*9,650,093.98*	*142,963,712.76*
	Rheumatic heart disease	542,927.14	373,763.62	1,239,211.09	794,823.04	902,529.46	464,535.36	263,561.84	66,074.80	4,647,426.36
	Hypertensive heart disease	80,843.40	46,059.61	225,566.63	756,894.20	1,941,117.67	1,863,497.03	1,443,421.58	550,912.48	6,908,312.61
	Ischaemic heart disease (CAD)	272,727.84	294,919.40	1,586,902.03	7,056,466.43	21,062,210.22	17,550,509.96	12,466,654.17	3,840,041.42	64,130,431.48
	Cerebrovascular disease	644,956.68	329,178.88	1,298,341.58	3,746,393.10	11,687,904.36	12,557,953.90	10,017,540.13	3,161,146.75	43,443,415.37
	Inflammatory heart diseases	500,347.47	166,691.39	772,137.43	1,124,333.76	1,240,197.93	784,042.36	560,767.98	207,291.94	5,355,810.26
	Other cardiovascular diseases	1,500,933.62	550,351.99	1,821,097.09	2,938,522.03	3,761,460.14	3,057,943.15	3,023,382.08	1,824,626.58	18,478,316.68
Female	*Cardiovascular diseases*	*4,322,292.12*	*2,043,699.48*	*6,515,640.21*	*10,578,754.65*	*27,406,391.57*	*31,842,342.77*	*35,168,560.99*	*18,227,567.25*	*136,105,249.03*
	Rheumatic heart disease	603,195.43	687,304.58	1,341,074.46	1,086,931.75	1,289,672.30	799,746.60	534,464.20	167,365.44	6,509,754.77
	Hypertensive heart disease	81,822.97	59,077.08	183,292.28	534,181.73	1,727,068.64	1,909,272.08	1,990,450.24	1,125,682.68	7,610,847.69
	Ischaemic heart disease (CAD)	232,696.48	197,380.29	1,790,133.99	3,693,401.62	11,009,195.44	13,826,324.43	13,928,748.72	6,612,270.71	51,290,151.68
	Cerebrovascular disease	541,859.55	289,058.48	964,054.22	2,711,239.00	9,268,449.82	11,412,033.79	13,366,898.74	6,481,309.66	45,034,903.26
	Inflammatory heart diseases	494,725.30	199,525.67	568,768.30	593,270.57	765,102.32	647,069.47	699,404.34	354,334.21	4,322,200.19
	Other cardiovascular diseases	2,367,992.37	611,353.38	1,668,316.95	1,959,729.99	3,346,903.05	3,247,896.40	4,648,594.75	3,486,604.56	21,337,391.44

Source: WHO (2002).

Table A.4.2. DALY – disability adjusted lost year (x1000s) by region, 2001 worldwide

CAUSE OF DISEASE	EASTERN MEDITERRANEAN		EUROPE			SOUTH–EAST ASIA		WESTERN PACIFIC		AFRICA		THE AMERICAS		
	Mortality stratum		Mortality stratum			Mortality stratum		Mortality stratum		Mortality stratum		Mortality stratum		
	Low child, low adult	High child, high adult	Very low child, very low adult	Low child, low adult	Low child, high adult	Low child, low adult	High child, high adult	Very low child, very low adult	Low child, low adult	High child, high adult	High child, very high adult	Very low child, very low adult	Low child, low adult	High child, high adult
*Population (*x *1000)*	*141,835*	*351,256*	*412,512*	*219,983*	*241,683*	*297,525*	*1,262,285*	*154,919*	*1,546,770*	*301,878*	*353,598*	*328,176*	*437,142*	*72,649*
	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*	*(*x *1000)*
Cardiovascular diseases	**280**	**757**	**1,760**	**1,111**	**2,171**	**571**	**3,226**	**395**	**3,350**	**5,388**	**5,976**	**6,950**	**7,194**	**1,001**
Rheumatic heart disease	3	21	11	8	15	9	123	3	105	359	405	42	108	11
Hypertensive heart disease	35	56	68	67	40	63	75	9	276	256	304	324	563	118
Ischaemic heart disease (CAD)	147	376	738	500	1,185	232	1,740	136	827	1,614	1,644	3,523	2,688	295
Cerebrovascular disease	47	171	456	296	728	193	877	163	1,763	1,508	1,810	1,448	2,332	277
Inflammatory heart disease	6	23	29	27	31	12	66	8	74	358	414	400	418	24
TOTAL DALYs	**707**	**3,449**	**4,076**	**1,969**	**3,658**	**2,194**	**12,273**	**1,161**	**10,475**	**147,899**	**209,985**	**46,520**	**81,270**	**17,427**

Source: WHO (2002).

Table A.4.3. Incidence of cardiovascular disease on total deaths, worldwide, Estimates for 2001

CAUSE OF DEATH	SEX					
	Both sexes		Males		Females	
Population (x 1000)	*6,122,210*		*3,083,884*		*3,038,327*	
	(x 1000)	*% total*	*(x 1000)*	*% total*	*(x 1000)*	*% total*
Cardiovascular diseases	**16,585**	**29.3**	**7,962**	**26.9**	**8,623**	**32.0**
Rheumatic heart disease	338	0.6	140	0.5	197	0.7
Hypertensive heart disease	874	1.5	397	1.3	477	1.8
Ischaemic heart disease (CAD)	7,181	12.7	3,756	12.7	3,425	12.7
Cerebrovascular disease	5,454	9.6	2,499	8.4	2,956	11.0
Inflammatory heart disease	375	0.7	192	0.6	183	0.7
TOTAL Deaths	**56,554**	**100.0**	**29,628**	**100.0**	**26,926**	**100.0**

Source: WHO (2002).

Table A.4.4. Total direct cost profile for a diabetic patients in Europe (2000)

Country	General healthcare cost per patient (US$)	Additional cost due to presence of diabetes (US$)	Annual cost per patient with type 2 diabetes (US$)
Belgium	1,495	1,647	3,142
France	1,979	1,009	2,988
Germany	2,146	1,330	3,476
Italy	1,259	1,611	2,870
Netherlands	1,634	180	1,814
Spain	1,046	241	1,287
Sweden	1,710	855	2,565
United Kingdom	1,144	881	2,025
Average	1,552	969	2,521

Source: International Diabetes Federation (2004).

Table A.4.5. CSII impact on Quality of Life parameters scale (0=poorest QoL, 100=highest QoL), as compared to MDI

	MDI	CSII	p-value
Social relations	79	85	0.025
Time flexibility	71	82	0.001
Physical complaints	68	81	0.000
Worries about future	37	51	0.010
Diet restrictions	60	77	0.001
Daily hassles	54	66	0.003
Fear of hypoglycaemia	54	68	0.000
Burdens of hypoglycaemic events	50	69	0.000
Blood glucose fluctuations	40	65	0.000
Self efficacy	70	79	0.001
Treatment satisfaction	51	71	0.000

Adapted from Linkeschova et al (2002)

Table A.4.6. Comparison of the results of the DCCT (1993) and the UKPDS (1998) studies with respect to intensive control of blood glucose levels

Risks (measures of outcome)	DCCT (1993)	UKPDS (1998)
HbA1c	9	
Retinopathy	Reduction of 63%	Reduction of 17-21%
Nephropathy	Reduction of 54%	Reduction of 24-33%
Neuropathy	Reduction of 60%	–
Macrovascular Disease	Reduction of 41%	Reduction of 16%

Table A.4.7. Cost per unit THR in Ireland

	Cost per unit THR
Salaries (including medical, nursing, physiotherapy, administrative, etc.)	£4,203.87
Materials	£641.19
Implant (FC 2 femur, Charnley cup)	£478.71
Medical equipment	£172.67
Laboratory/Radiology costs	£155.72
Maintenance charges	£207.56
Provisions	£114.37
Housekeeping	£214.72
Administration	£200.79
Miscellaneous	£82.46
Total	**£6,472.06**

Adapted from O'Shea et al (2002)

Table A.4.8. Percentage probability of developing breast cancer from age on the rows to age on the columns, years 1991-2001, US female population

	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	95+
0	0.00	0.00	0.00	0.00	0.01	0.05	0.18	0.48	1.05	1.93	3.09	4.54	6.18	7.90	9.57	11.10	12.24	12.97	13.27	13.39
5		0.00	0.00	0.00	0.01	0.05	0.18	0.49	1.06	1.95	3.12	4.59	6.25	7.98	9.67	11.21	12.37	13.11	13.41	13.53
10			0.00	0.00	0.01	0.05	0.18	0.49	1.06	1.95	3.12	4.59	6.25	7.99	9.68	11.22	12.38	13.12	13.42	13.54
15				0.00	0.01	0.05	0.18	0.49	1.06	1.95	3.12	4.60	6.25	7.99	9.69	11.23	12.39	13.13	13.43	13.55
20					0.01	0.05	0.18	0.49	1.06	1.95	3.13	4.60	6.26	8.00	9.70	11.25	12.41	13.14	13.45	13.57
25						0.04	0.17	0.48	1.05	1.95	3.12	4.60	6.27	8.01	9.71	11.26	12.43	13.16	13.46	13.59
30							0.13	0.44	1.01	1.91	3.09	4.57	6.24	7.99	9.69	11.25	12.42	13.16	13.46	13.59
35								0.31	0.88	1.78	2.97	4.46	6.14	7.89	9.60	11.16	12.34	13.08	13.38	13.51
40									0.58	1.49	2.68	4.18	5.87	7.64	9.37	10.94	12.12	12.87	13.18	13.31
45										0.92	2.13	3.65	5.36	7.16	8.90	10.50	11.70	12.45	12.76	12.89
50											1.24	2.79	4.53	6.36	8.14	9.77	10.99	11.76	12.08	12.21
55												1.59	3.39	5.27	7.11	8.78	10.04	10.83	11.16	11.29
60													1.87	3.84	5.75	7.49	8.80	9.63	9.97	10.11
65														2.08	4.12	5.97	7.36	8.24	8.60	8.75
70															2.22	4.24	5.77	6.73	7.12	7.29
75																2.31	4.04	5.14	5.59	5.78
80																	2.12	3.46	4.01	4.24
85																		1.86	2.63	2.95
90																			1.34	1.91
95																				1.28

Source: Fay (2003).

Table A.4.9. Estimated Breast Cancer Cases/Deaths Worldwide. Source Ferlay et al (2001)

Region	New Cases (2000)	Deaths (2000)
Eastern Africa	13,615	6,119
Middle Africa	3,902	1,775
Northern Africa	18,724	8,388
Southern Africa	5,537	2,504
Western Africa	17,389	7,830
Caribbean	6,210	2,310
Central America	18,663	5,888
South America	69,924	22,735
Northern America	202,044	51,184
Eastern Asia	142,656	38,826
South–Eastern Asia	55,907	24,961
South Central Asia	129,620	62,212
Western Asia	20,155	8,459
Eastern Europe	110,975	43,058
Northern Europe	54,551	20,992
Southern Europe	65,284	25,205
Western Europe	115,308	40,443
Australia/New Zealand	12,748	3,427
Melanesia	470	209
Micronesia	62	28
Polynesia	127	58

Table A.4.10. A history of Breast Cancer screening

William Roentgen discovered X-rays	*1894*
Albert Salomon (pathologist in Berlin) produced images of 3.000 gross mastectomy specimens, observing black spots at the centres of breast carcinomas	*1913*
Jacob Gershon–Cohen (Jefferson Medical College, PA) thought studying the normal breast 'under all conditions of growth and physiology' would improve understanding of the cancerous breast	*1930s*
Stafford Warren (Rochester Memorial Hospital, NY) developed a stereoscopic system for tumour identification	*1940s*
Raul Lebrogne (Uruguay) emphasised breast compression for identification of calcifications	*1949*
Breast Self–Examination (BSE) advocated	*1940s, 1950s*
Charles Gros (France) developed a radiological unit designed for breast examinations	*1951*
Robert Egan (US) adapted high–resolution industrial film for mammography, allowing simple and reproducible mammograms.	*1960*
First randomised trial of screening by the **Health Insurance Plan of New York** (HIP Trial) found that mammography reduced the 5–year BC mortality by 30%	*1963*
Siemens, Philips and Picker began selling special mammography systems. Philips' device set as new standard	*1970s*
Xerox technology was coupled with mammography, replacing traditional X-ray film with an electrically charged selenium–coated aluminium plate	*1971*
Breast Cancer Detection Demonstration Project (BCDDP) began in 29 US centres	*1973*
Malmoe Trial on breast screening by mammography	*1976*
NIH Consensus Conference on BC screening	*1977*
Trial of Early Detection of Breast Cancer (TEDBC) in the U.K.	*1979*
Canadian National Breast Cancer Studies (CNBCS)	*1980*
Stockholm Trial on breast screening by mammography	*1981*
Gothenburg Trial on breast screening by mammography	*1983*
The American College of Radiology developed breast screening accreditation program for radiologists and technicians	*1986*
Joint Guidelines issued for mammography screening by American College of Radiology and NCI	*1988*
International Breast Cancer Screening Network (IBCSN) established to assess screening programs	*1990*
Mammography Quality Standards ACT passed	*1992*
NCI International Workshop on mammography trials	*1993*
Major improvements in mammography equipments include reduced radiation dosage, automatic exposure controls, better films, film emulsifiers, digital imaging, computer aided detection	*1980s, 1990s*

Sources: Gold et al (1990), Institute of Medicine – National Research Council (2001), Lerner (2001)

Table A.4.11. Most recent developments in imaging devices

Technology	Description, mechanism	Potential strengths	Current limitations
Digital Mammography	Detector responds to X-ray exposure, sends electronic signal to computer to be digitised and processed. Separates detector and image display.	Ability to manipulate contrast and magnification with one exposure. Ease of image storage & retrieval. Facilitates CAD, digital tomo-synthesis, and tele-mammography	Spatial resolution and luminance of digital display are lower than standard film–screen mammography. Old film–screen difficult to digitalise for comparison
Computer Aided Detection and Diagnosis (CAD)	Computer programs to aid in identification of suspicious mammograms and classification as benign or malignant. Serves as a second opinion to radiologists	Retrospective studies show that CAD can improve radiologists' readings and improve rate of false–negative results	CAD used alone has very low specificity. Sensitivity & specificity are undetermined for general screening population
Ultrasound	Use of high–frequency sound waves to generate an image	Studies suggest potential for increased use in diagnosis and perhaps even screening, especially for women with dense breasts	Poor ability to detect microcalcifications due to speckle. Compound imaging may help reduce speckle
Magnetic Resonance Imaging (MRI)	Image generated by signals from excitation of nuclear particles in magnetic field. Breast tumour show increased uptake of contrast agent	Benefits in detection are detection of multiple malignancies; detection of invasive carcinoma; screening for high–risk women with dense breasts; detection of recurrent cancers	Lack of uniform interpretation criteria. Cannot reliably detect microcalcifications and small tumours, especially if they do not pick up the contrast agent. Overlap in uptake time course of benign and malignant tumours

Adapted from Institute of Medicine – National Research Council (2001)

Table A.4.12. Screening tests for women at different ages, recommendations and benefits

Age	Recommendation	Benefit
Age 40 to 49	Mammogram every 1 to 2 years, with or without clinical breast exam	May reduce risk of dying from breast cancer by 17%
Age 50 to 74	Mammogram every 1 to 2 years, with or without clinical breast exam	May reduce risk of dying from breast cancer by 30%

Source: USPSTF (2004).

ANNEX TO CHAPTER 5

Table A.5.1. Production value (constant 1995 € millions), and share of production value in manufacturing total (%), MD (NACE 33.1), 1997-2002

	1997		1998		1999		2000		2001		2002	
	€	%	€	%	€	%	€	%	€	%	€	%
Austria	586	0.7	660	0.7	655	0.7	421	0.4	464	0.5	459	0.4
Belgium	543	0.4	574	0.4	370	0.3	481	0.3	422	0.2	n.a.	n.a.
Denmark	752	1.3	792	1.3	778	1.3	826	1.3	945	1.4	987	1.5
Finland	522	0.7	579	0.8	595	0.7	663	0.7	757	0.8	773	0.9
France	4355	0.6	4313	0.6	4616	0.6	4873	0.6	5364	0.7	5458	0.6
Germany	n.a.	n.a.	n.a.	n.a.	14183	1.1	11847	0.9	12417	0.9	13048	1.0
Ireland	988	n.a.	1032	n.a.	1394	2.2	1965	2.6	2755	3.8	2888	4.1
Italy	2509	0.4	2784	0.5	2498	0.5	2916	0.5	3219	0.5	3238	0.5
Luxembourg	13	0.2	11	0.2	14	n.a.	15	0.2	15	0.2	15	0.2
Netherlands	1164	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Portugal	80	0.1	106	0.2	89	0.2	80	0.1	77	0.1	n.a.	n.a.
Spain	414	0.2	527	0.2	557	0.2	578	0.2	747	0.2	870	0.3
Sweden	1032	0.9	1097	0.9	1062	0.8	1304	1.0	1461	1.1	n.a.	n.a.
UK	2194	0.5	2238	0.5	2418	0.5	2242	0.5	2416	0.5	n.a.	n.a.
Cyprus	4	0.2	3	0.2	n.a.	n.a.	3	0.1	4	0.2	4	0.2
Czech Rep.	127	0.3	186	0.5	158	0.5	132	0.3	145	n.a.	166	0.4
Estonia	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	9	0.4	11	0.5
Hungary	n.a.	n.a.	85	0.3	125	0.5	80	0.2	111	0.3	119	0.3
Latria	3	0.1	4	0.2	5	0.3	4	0.2	4	0.2	n.a.	n.a.
Lithuania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	9	0.3	15	0.5	15	0.5
Malta	n.a.	n.a.	n.a.	n.a.	20	1.0	23	0.9	n.a.	n.a.	n.a.	n.a.
Poland	183	0.3	186	0.3	238	0.3	253	0.3	258	0.3	301	0.4
Slovak Rep.	37	0.4	30	0.3	n.a.	n.a.	31	0.2	44	0.3	50	0.4
Slovenia	18	0.2	17	0.1	16	0.1	18	0.1	23	0.2	38	0.3
Bulgaria	8	0.1	9	0.1	8	0.2	8	0.1	8	0.1	8	0.1
Norway	199	0.5	205	0.4	220	0.5	195	0.5	198	0.5	n.a.	n.a.
Romania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	9	0.1	11	0.1	11	0.1

Source: Eurostat (2004).

Table A.5.2. Value added at factor cost (constant 1995 € millions), and share of value added in manufacturing total (%), MD (NACE 33.1), 1997-2002

	1997		1998		1999		2000		2001		2002	
	€	%	€	%	€	%	€	%	€	%	€	%
Austria	296	0.9	349	1.0	337	1.0	238	0.7	247	0.7	278	0.8
Belgium	165	0.4	163	0.4	159	0.4	180	0.4	152	0.4	n.a.	n.a.
Denmark	344	1.6	397	1.8	369	1.7	390	1.7	443	1.9	467	2.1
Finland	273	1.2	278	1.1	304	1.2	311	1.1	341	1.2	342	1.2
France	1851	1.0	1781	1.0	1918	1.0	2013	1.0	2196	1.1	2119	1.1
Germany	n.a.	n.a.	n.a.	n.a.	7793	1.8	6057	1.5	6415	1.6	6556	1.7
Ireland	508	2.9	487	2.7	671	3.0	1050	4.0	1230	5.0	1246	4.9
Italy	1175	0.8	1132	0.7	1126	0.7	1327	0.8	1224	0.8	1346	0.9
Luxembourg	7	0.4	6	0.3	6	n.a.	10	0.5	6	0.3	7	0.4
Netherlands	482	1.0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Portugal	30	0.2	40	0.3	35	0.2	34	0.2	31	0.2	n.a.	n.a.
Spain	191	0.2	242	0.3	261	0.3	284	0.3	340	0.4	376	0.4
Sweden	421	1.1	389	1.0	355	0.9	440	1.1	429	1.1	n.a.	n.a.
UK	1038	0.6	1128	0.7	1273	0.8	1192	0.8	1199	0.8	n.a.	n.a.
Cyprus	2	0.3	2	0.3	n.a.	n.a.	2	0.3	2	0.3	2	0.3
Czech Rep.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	58	0.6	58	0.6	73	0.7
Estonia	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3	0.6	4	0.6
Hungary	n.a.	n.a.	33	0.5	41	0.6	9	0.1	44	0.6	50	0.6
Latria	1	0.2	1	0.2	3	0.5	2	0.3	2	0.2	n.a.	n.a.
Lithuania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3	0.5	-5	-0.8	5	0.7
Malta	n.a.	n.a.	n.a.	n.a.	12	2.1	14	2.0	n.a.	n.a.	n.a.	n.a.
Poland	98	0.4	103	0.4	130	0.5	121	0.5	139	0.5	138	0.5
Slovak Rep.	12	0.6	12	0.5	n.a.	n.a.	11	0.4	17	0.5	20	0.7
Slovenia	7	0.2	7	0.2	6	0.2	7	0.2	9	0.2	13	0.3
Bulgaria	n.a.	n.a.	n.a.	n.a.	3	0.2	3	0.2	3	0.3	3	0.3
Norway	81	0.6	78	0.5	93	0.7	78	0.6	73	0.5	n.a.	n.a.
Romania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	4	0.1	5	0.1	4	0.1

Source: Eurostat (2004).

Table A.5.3. Number of employees, and share of employment in manufacturing total (%), MD (NACE 33.1), 1997-2002

	1997		1998		1999		2000		2001		2002	
	n	%	n	%	n	%	n	%	n	%	n	%
Austria	7405	1.2	8054	1.3	7322	1.2	6081	1.0	6249	1.0	6335	1.0
Belgium	3168	0.5	3311	0.5	3167	0.5	3005	0.5	2980	0.5	n.a.	n.a.
Denmark	n.a.	n.a.	7762	1.6	6466	1.4	6676	1.4	7142	1.5	7397	1.6
Finland	4402	1.1	4734	1.1	5139	1.2	5377	1.3	5115	1.2	5156	1.2
France	39155	1.0	40095	1.0	40611	1.0	39762	1.0	42527	1.1	43297	1.1
Germany	n.a.	n.a.	n.a.	n.a.	140199	1.9	141022	1.9	145037	2.0	140328	2.0
Ireland	9503	n.a.	10194	n.a.	11484	4.6	12936	5.1	14770	5.9	15093	6.3
Italy	25624	0.6	25721	0.6	26080	0.7	28728	0.7	25692	0.6	26769	0.7
Luxembourg	271	0.8	284	0.8	278	n.a.	288	0.9	290	0.9	301	0.9
Netherlands	10228	n.a.	9949	n.a.	9890	1.2	10698	1.2	n.a. c	n.a.	10742	1.3
Portugal	1891	0.2	2670	0.3	2011	0.2	2005	0.2	2223	0.3	n.a.	n.a.
Spain	7488	0.3	8899	0.4	8154	0.4	8593	0.4	11845	0.5	13014	0.5
Sweden	8330	1.1	8342	1.1	8268	1.1	9043	1.2	9356	1.2	n.a.	n.a.
UK	28247	0.7	31458	0.7	30092	0.7	29844	0.8	35082	0.9	n.a.	n.a.
Cyprus	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	112	0.3	n.a.	n.a.	n.a.	n.a.
Czech Rep.	7980	0.6	8924	0.7	8052	0.6	7168	0.6	8649	n.a.	8613	0.7
Estonia	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a. c	n.a.	528	0.4	685	0.5
Hungary	n.a.	n.a.	4653	0.6	4775	0.6	4993	0.7	7019	0.8	7682	0.9
Latria	503	0.3	449	0.3	530	0.4	568	0.4	564	0.4	n.a.	n.a.
Lithuania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1206	0.5	1415	0.6	1451	0.6
Malta	n.a.	n.a.	n.a.	n.a.	484	1.7	502	1.7	n.a. c	n.a.	n.a.	n.a.
Poland	8573	0.3	9378	0.4	10368	0.4	10654	0.5	10621	0.5	12675	0.6
Slovak Rep.	3616	0.8	2477	0.6	n.a. c	n.a.	2139	0.5	2600	0.6	2764	0.7
Slovenia	730	0.3	721	0.3	671	0.3	707	0.3	827	0.3	1010	0.4
Bulgaria	2044	0.3	2181	0.3	2133	0.3	2342	0.4	1977	0.3	1996	0.3
Norway	1851	0.6	1801	0.6	1927	0.7	1804	0.6	1750	0.6	n.a.	n.a.
Romania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2015	0.1	2008	0.1	2067	0.1

Source: Eurostat (2004).

Table A.5.4. Gross value added per person employed (apparent labour productivity)

Country	1997	1998	1999	2000	2001	2002
Austria	37.2	40.9	43.0	35.7	36.3	40.1
Belgium	37.3	35.2	35.6	40.5	36.5	n.a.
Denmark	41.0	50.1	55.8	57.2	60.9	62.2
Finland	59.7	57.2	57.8	56.6	65.2	64.0
France	42.4	40.0	42.6	45.8	47.1	44.8
Germany	n.a.	n.a.	55.2	42.7	41.7	43.7
Ireland	53.4	47.7	58.4	81.1	83.3	82.6
Italy	22.9	22.0	22.6	26.3	24.9	27.5
Luxembourg	25.2	21.0	20.7	32.1	21.3	22.7
Netherlands	38.9	n.a.	n.a.	n.a.	n.a.	n.a.
Portugal	13.8	13.4	14.3	14.3	11.3	n.a.
Spain	19.2	23.4	22.3	24.1	22.2	22.5
Sweden	48.3	44.6	n.a.	46.1	43.5	n.a.
UK	33.7	34.7	40.8	38.9	33.0	n.a.
Cyprus	n.a.	n.a.	n.a.	13.8	14.2	13.0
Czech Rep.	n.a.	n.a.	n.a.	n.a.	5.6	6.8
Estonia	n.a.	n.a.	n.a.	n.a.	6.5	5.6
Hungary	n.a.	n.a.	n.a.	1.8	5.4	5.2
Latria	n.a.	n.a.	5.7	3.5	4.0	n.a.
Lithuania	n.a.	n.a.	n.a.	2.6	-3.4	3.1
Malta	n.a.	n.a.	25.1	27.5	n.a.	n.a.
Poland	n.a.	n.a.	n.a.	n.a.	n.a.	6.5
Slovak Rep.	n.a.	n.a.	n.a.	5.1	6.6	7.3
Slovenia	n.a.	n.a.	n.a.	n.a.	n.a.	12.4
Albania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Bulgaria	n.a.	n.a.	n.a.	n.a.	1.2	1.3
Norway	42.1	41.7	47.1	42.4	41.4	n.a.
Romania	n.a.	n.a.	n.a.	2.0	2.3	2.0

Source: Eurostat (2004).

Table A.5.5. International Trade, MD (CN 9018, 9019, 9021, 9022, 9402), 1988-2001, € mil

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
EXPORTS FROM EU TO														
INTRA EU-15	2,903	3,304	3,656	4,170	4,672	4,727	5,187	7,165	8,341	8,809	9,604	10,866	12,345	13,296
EXTRA EU-15	3,444	3,764	3,976	4,506	4,902	5,739	6,144	6,530	7,138	8,094	8,836	9,962	12,284	14,874
Switzerland	202	230	244	257	261	264	288	332	345	366	402	505	560	678
Norway	59	63	66	74	77	77	79	134	157	181	208	228	251	265
Iceland	4	4	4	5	5	5	5	6	8	9	9	12	15	26
New Member States[60]	108	132	137	194	241	293	367	450	504	563	586	604	769	860
US	1,114	1,117	1,115	1,415	1,475	1,571	1,492	1,715	1,776	2,093	2,581	3,340	4,023	5,177
Japan	268	306	322	340	376	467	490	709	761	927	890	1,111	1,385	1,448
Rest of the world	1,689	1,913	2,088	2,220	2,467	3,061	3,423	3,183	3,586	3,956	4,159	4,162	5,281	6,421
Extra/Intra EU-15	1.19	1.14	1.09	1.08	1.05	1.21	1.18	0.91	0.86	0.92	0.92	0.92	1.00	1.12
IMPORTS TO EU FROM														
INTRA EU-15	3,009	3,433	3,926	4,451	4,937	4,581	5,088	6,820	7,863	8,298	9,396	10,140	11,685	12,233
EXTRA EU-15	2,624	3,170	3,343	4,046	4,355	4,636	4,978	5,222	5,958	6,949	7,484	9,251	11,143	12,936
Switzerland	378	384	429	507	551	561	617	752	780	781	910	1,147	1,400	1,706
Norway	21	24	26	30	33	38	41	52	53	61	64	70	68	71
Iceland	0,4	0,1	0,1	0,3	0,5	0,7	1,3	2,1	2,8	3,8	5	6	9	10
New Member States[61]	8	8	10	20	32	34	50	87	106	116	191	224	226	312
US	1,213	1,584	1,640	2,027	2,146	2,354	2,579	2,979	3,537	4,307	4,399	5,347	6,639	7,881
Japan	530	618	619	708	735	723	676	738	725	737	833	1,073	1,077	1,130

[60] Time series start from 1992 for Slovenia, Estonia, and Lithuania, and from 1993 for Latvia and Poland.

[61] Data for Czech Republic are missing for the time period 1988-1990. Time series start from 1992 for Slovenia (the year in which its independence was recognised), from 1994 for Cyprus, from 1995 for Estonia, from 1996 for Lithuania, and from 1997 for Latvia. Data for Malta are missing in 2000.

		1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Rest of the world		473	552	619	754	859	925	1,014	611	754	943	1,083	1,385	1,724	1,826
Extra/Intra EU-15		0.87	0.92	0.85	0.91	0.88	1.01	0.98	0.77	0.76	0.84	0.80	0.91	0.95	1.06
TRADE BALANCE															
EXTRA EU-15		821	594	633	461	546	1,103	1,167	1,308	1,180	1,146	1,352	711	1,141	1,938
EXTRA Export/Import ratio	EU-15	1.31	1.19	1.19	1.11	1.13	1.24	1.23	1.25	1.20	1.16	1.18	1.08	1.10	1.15

Source: Eurostat (2005).

Table A.5.6. Medical Specialty in the FDA product listing

Medical Specialty	Code	Medical Specialty	Code
Anaesthesiology	an	Immunology	im
Cardiovascular	cv	Microbiology	mi
Clinical Chemistry	ch	Neurology	ne
Clinical Toxicology	tx	Obstetrics-Gynecology	ob
Dental	de	Ophthalmic	op
Ear, Nose, Throat	en	Orthopedic	or
General and Plastic Surgery	su	Pathology	pa
General Hospital	ho	Physical Medicine	pm
Gastroenterology/Urology	gu	Radiology	ra
Hematology	he		

ANNEX TO CHAPTER 6

Table A.6.1. R&D expenditures, MD, million € and ratio with respect to turnover

	1995		1996		1997		1998		1999		2000		2001		2002	
	€	% turn.	€	% turn.	€	% turn.	€	% turn.	€	% turn.	€	% turn.	€	% turn.	€	% turn.
Belgium	0.5	0.11	0.0	0.00	n.a.	n.a.	4.4	0.78	3.8	0.65	0.4	0.07	0.4	0.09	n.a.	n.a.
Czech Rep.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.5	0.27
Germany	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	336.3	2.19	348.6	2.69	363.7	2.69	364.6	2.54
Estonia	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.0	0.00	0.0	0.00
Spain	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	5.9	0.97	10.5	1.59	n.a.	n.a.	n.a.	n.a.
France	n.a.	n.a.	n.a.	n.a.	92.8	1.86	93.9	1.90	113.6	2.15	117.2	2.12	128.1	2.13	132.9	2.14
Italy	n.a.	n.a.	n.a.	n.a.	39.2	1.51	40.1	1.35	36.9	1.37	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Cyprus	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0,0	0,00	0,0	0,00	0,0	0,00
Latria	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Lithuania	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0,0	0,00	0,1	0,98
Luxembourg	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0,0	0,00	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hungary	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.7	0.68	0.5	0.37	0.4	0.46	0.3	0.23	0.6	0.40
Malta	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.1	0.39	0.1	0.34	n.a.	n.a.	n.a.	n.a.
Austria	6.2	1.42	n.a.	n.a.	8.9	1.36	9.0	1.24	9.9	1.36	11.4	2.38	14.1	2.73	11.0	2.17
Poland	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Portugal	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.4	0.48	0.1	0.10	0.0	0.00	n.a.	n.a.
Slovenia	0	0.00	n.a.	n.a.	0.1	0.48	0.1	0.47	n.a.	n.a.	0.1	0.43	0.4	1.32	0.4	1.08
Slovak Rep.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.5	1.30	0.6	1.15	0.4	0.77
Finland	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.0	0.00
UK	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	28.5	1.15	38.1	1.40	48.1	1.87	56.5	2.14	n.a.	n.a.
Norway	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.0	0.00	n.a.	n.a.

Source: Eurostat (2004).

Table A.6.2. Employees size distribution, firms included in the analysis, 2002

	Number of firms				Share of firms (%)			
Number of employees	1-49	50-249	250-749	>750	1-49	50-249	250-749	>750
325413: In-Vitro Diagnostic Substance Manufacturing	5	16	13	11	11.11	35.56	28.89	24.44
339111: Laboratory Apparatus and Furniture Manufacturing (pt)	0	4	2	2	0.00	50.00	25.00	25.00
339112: Surgical and Medical Instrument Manufacturing (pt)	10	14	21	15	16.67	23.33	35.00	25.00
339113: Surgical Appliance and Supplies Manufacturing	6	3	14	21	13.64	6.82	31.82	47.73
334510: Electromedical and Electrotherapeutic Apparatus Manufacturing (pt)	8	32	33	17	8.89	35.56	36.67	18.89
339114: Dental Equipment and Supplies Manufacturing	1	1	3	3	12.50	12.50	37.50	37.50
339115: Ophthalmic Goods Manufacturing (pt)	0	0	1	6	0.00	0.00	14.29	85.71
334517: Irradiation Apparatus Manufacturing (pt)	1	1	4	3	11.11	11.11	44.44	33.33
Total	31	71	91	78	11.44	26.20	33.58	28.78

Source: our elaborations on Standard & Poor's Compustat® (2004b).

Table A.6.3. R&D Intensity Percentiles[62] (indicating the share of firms that have R&D intensity greater than or equal to…), North-American Companies

		1993				1997				2002			
NAICS	Description	N.Obs.	75%	50%	25%	N.Obs.	75%	50%	25%	N.Obs.	75%	50%	25%
325413	In-Vitro Diagnostic Substance Manufacturing	46	7.72	18.12	182.89	64	10.01	58.38	253.28	47	11.37	49.97	221.36
339111	Laboratory Apparatus and Furniture Manufacturing (pt)	9	0.61	2.19	5.83	8	3.82	6.51	6.94	7	5.19	6.22	13.25
339112	Surgical and Medical Instrument Manufacturing (pt)	58	3.74	6.20	18.05	74	6.28	13.36	62.13	56	5.31	9.31	51.37
339113	Surgical Appliance and Supplies Manufacturing	50	2.10	5.46	10.67	47	3.17	5.80	21.90	40	1.82	4.57	6.22
339114	Dental Equipment and Supplies Manufacturing	7	1.91	2.52	17.86	10	2.27	4.36	7.55	9	1.91	5.77	13.07
339115	Ophthalmic Goods Manufacturing (pt)	7	3.51	5.69	11.97	10	2.02	3.31	4.25	7	1.91	2.17	7.06
334510	Electromedical and Electrotherapeutic Apparatus Manufacturing (pt)	99	5.73	10.98	32.56	107	7.80	13.42	55.75	86	7.34	12.18	22.11
334517	Irradiation Apparatus Manufacturing (pt)	11	7.19	8.69	12.83	15	8.42	10.77	29.18	9	4.19	8.7132	11.33
	Total	287	4.07	8.14	21.94	335	6.28	12.36	60.99	261	5.03	10.06	25.97

Source: Our elaborations on Standard & Poor's Compustat® (2004b).

[62] The percentile identifies the value that divides the cases according to a threshold below which a certain percentage of cases fall. For example, the 75th percentile corresponds to the value below which 75 percent of the cases fall.

Table A.6.4. Number of R&D licensing agreements in MD, by country of licensor and licensee

	As licensor		Partner location (%)				As licensee		Partner location (%)			
	N	%	Europe	Japan	Other	US and Canada	N	%	Europe	Japan	Other	US and Canada
US	1487	73.8	15.2	3.0	1.3	80.4	1441	71.5	12.2	0.9	2.8	84.0
Japan	26	1.3	15.4	30.8	3.8	50.0	70	3.5	14.3	11.4	4.3	70.0
Canada	82	4.1	11.0	4.9	0.0	84.1	65	3.2	13.8	0.0	3.1	83.1
Denmark	10	0.5	50.0	0.0	10.0	40.0	14	0.7	28.6	0.0	14.3	57.1
Finland	2	0.1	0.0	0.0	0.0	100.0	6	0.3	0.0	0.0	0.0	100.0
France	27	1.3	37.0	0.0	0.0	63.0	12	0.6	50.0	0.0	8.3	41.7
Germany	73	3.6	43.8	0.0	1.4	54.8	97	4.8	39.2	0.0	5.2	55.7
Ireland	8	0.4	12.5	0.0	0.0	87.5	9	0.4	33.3	0.0	0.0	66.7
Italy	6	0.3	33.3	33.3	0.0	33.3	8	0.4	12.5	25.0	0.0	62.5
Netherlands	14	0.7	57.1	14.3	14.3	14.3	19	0.9	31.6	0.0	5.3	63.2
Norway	2	0.1	100.0	0.0	0.0	0.0	3	0.1	100.0	0.0	0.0	0.0
Sweden	12	0.6	50.0	0.0	0.0	50.0	14	0.7	50.0	0.0	0.0	50.0
Switzerland	34	1.7	26.5	5.9	0.0	67.6	82	4.1	25.6	0.0	6.1	68.3
UK	136	6.7	44.1	2.9	1.5	51.5	121	6.0	41.3	1.7	3.3	53.7
Other EU	22	1.1	45.5	0.0	0.0	54.5	17	0.8	35.3	0.0	0.0	64.7
Other	75	3.7	24.0	4.0	14.7	57.3	38	1.9	15.8	2.6	28.9	52.6
Total	2016	100.0					2016	100.0				

Source: ATA (2004).

Table A.6.5. US Patents, by nationality of first inventor

	1974-1983		1984-1993		1994-1998		1999-2003		1974-2003	
Country	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
US	7952	73.81	17645	70.83	18558	79.81	38879	72.02	83034	73.53
EU15	1134	10.53	3642	14.62	3139	13.50	7184	13.31	15099	13.37
NMS	26	0.24	53	0.21	26	0.11	44	0.08	149	0.13
EU25	1160	10.77	3695	14.83	3165	13.61	7228	13.39	15248	13.50
Japan	392	3.64	2171	8.71	162	0.70	3447	6.38	6172	5.47
Germany	421	3.91	1421	5.70	1076	4.63	2496	4.62	5414	4.79
France	230	2.13	578	2.32	501	2.15	1031	1.91	2340	2.07
UK	183	1.70	606	2.43	456	1.96	1063	1.97	2308	2.04
Canada	141	1.31	315	1.26	344	1.48	801	1.48	1601	1.42
Israel	40	0.37	182	0.73	204	0.88	1068	1.98	1494	1.32
Sweden	63	0.58	350	1.40	371	1.60	642	1.19	1426	1.26
Switzerland	109	1.01	311	1.25	231	0.99	626	1.16	1277	1.13
Netherlands	78	0.72	151	0.61	222	0.95	518	0.96	969	0.86
Italy	64	0.59	215	0.86	192	0.83	446	0.83	917	0.81
Australia	63	0.58	190	0.76	161	0.69	391	0.72	805	0.71

Source: ATA (2004).

Table A.6.6. US Patents and Publications, by nationality of assignee (patents) and main author's institution (publications)

	Patents								Publications							
	1974-83		1984-93		1994-98		1999-2003		1974-1983		1984-1993		1994-1998		1999-2003	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
US	6317	75.32	17935	72.15	18989	77.50	25148	74.12	108	45.38	28336	39.26	33297	39.74	38060	35.68
EU15	1217	14.51	3251	13.08	2678	10.93	4193	12.36	87	36.55	26573	36.81	29615	35.34	37907	35.53
NMS	23	0.27	52	0.21	20	0.08	30	0.09	3	1.26	556	0.77	634	0.76	1118	1.05
EU25	1240	14.78	3303	13.29	2698	11.01	4223	12.45	90	37.82	27129	37.58	30249	36.10	39025	36.58
Japan	484	5.76	2219	8.93	1569	6.40	2052	6.05	5	2.10	5682	7.87	7143	8.52	8522	7.99
Germany	536	6.39	1309	5.26	938	3.83	1472	4.34	16	6.72	5692	7.89	6848	8.17	9169	8.59
UK	291	3.47	544	2.19	369	1.50	530	1.56	16	6.72	6678	9.25	7211	8.61	8690	8.15
France	162	1.93	504	2.03	431	1.76	594	1.75	19	7.98	3110	4.31	3468	4.14	4214	3.95
Switzerland	102	1.21	371	1.49	225	0.92	533	1.57	9	3.78	1445	2.00	1539	1.84	1819	1.71
Canada	62	0.74	296	1.19	310	1.26	464	1.37	7	2.94	2977	4.12	3090	3.69	3270	3.07
Sweden	78	0.93	271	1.09	337	1.38	434	1.28	3	1.26	2132	2.95	1945	2.32	1936	1.81
Netherlands	56	0.67	166	0.67	156	0.64	450	1.33	1	0.42	1982	2.75	2173	2.59	2647	2.48
Israel	33	0.39	165	0.66	180	0.74	435	1.28	2	0.84	809	1.12	774	0.92	1100	1.03
Italy	36	0.43	190	0.76	172	0.70	215	0.63	20	8.40	1978	2.74	2508	2.99	3758	3.52
Australia	47	0.56	154	0.62	139	0.57	211	0.62	2	0.84	1689	2.34	1907	2.28	2315	2.17
Total	8284	98.77	24441	98.33	24110	98.40	33066	97.45	223	98.06	223	93.70	68067	94.30	77999	93.09
Total (a)	10799	100.00	24912	100.00	24675	100.00	53792	100.00	238	100.00	72183	100.00	83792	100.00	106681	100.00
Unknown (b)	2412		56		174		49		120743		110697		28409		286314	

(a) with known assignee/affiliation. (b) The share is computed over the total number of patents/publications.

Source: ATA (2004).

Table A.6.7. Citation received (US Patents), by nationality of assignee; Total Impact Factor (Publications), by nationality of institution

	Patents								Publications							
	1974-83		1984-93		1994-98		1999-2003		1974-1983		1984-1993		1994-1998		1999-2003	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
US	143251	78.85	478309	79.78	298958	84.85	81966	83.95	228	71.73	59337	48.97	69887	46.36	77151	40.78
EU15	20799	11.45	56545	9.43	26413	7.50	7503	7.68	70	21.97	37343	30.82	49923	33.11	66792	35.30
NMS	333	0.18	627	0.10	165	0.05	40	0.04	0	0.00	500	0.41	697	0.46	1391	0.73
EU25	21132	11.63	57172	9.54	26578	7.54	7543	7.73	70	21.97	37843	31.23	50619	33.58	68183	36.04
Japan	9748	5.37	36656	6.11	13830	3.93	3226	3.30	4	1.25	7282	6.01	10541	6.99	13898	7.35
Germany	9351	5.15	21943	3.66	9076	2.58	2426	2.48	9	2.96	5823	4.81	10080	6.69	15477	8.18
UK	4508	2.48	9223	1.54	3800	1.08	1497	1.53	21	6.53	11213	9.25	12649	8.39	14938	7.90
France	2801	1.54	8715	1.45	5595	1.59	1125	1.15	10	3.28	4559	3.76	6316	4.19	8275	4.37
Switzerland	2138	1.18	8655	1.44	2358	0.67	961	0.98	6	1.98	1863	1.54	2486	1.65	3194	1.69
Canada	1689	0.93	5809	0.97	3320	0.94	1239	1.27	6	2.03	6077	5.02	6126	4.06	6509	3.44
Sweden	1345	0.74	4918	0.82	2321	0.66	716	0.73	17	5.42	2986	2.46	3131	2.08	3302	1.75
Israel	781	0.43	3114	0.52	2575	0.73	844	0.86	1	0.25	1193	0.98	1513	1.00	1963	1.04
Netherlands	1039	0.57	3596	0.60	1643	0.47	425	0.44	0	0.00	3528	2.91	4739	3.14	5543	2.93
Australia	1195	0.66	2897	0.48	1589	0.45	412	0.42	2	0.55	2855	2.36	2778	1.84	3821	2.02
Italy	594	0.33	3648	0.61	1455	0.41	371	0.38	2	0.51	2763	2.28	4371	2.90	6124	3.24
Total	179934	99.04	592612	98.85	349208	99.11	96191	98.52	318	99.75	116450	96.11	143950	95.48	174718	92.35
Total (a)	180592	100.00	597812	100.00	352130	100.00	103846	100.00	318	100.00	121162	100.00	150760	100.00	189194	100.00
Unknown (b)	43728		952		2581		314		173448		137176		39118		33452	

(a) with known assignee/affiliation. (b) The share is computed over the total number of patents/publications.
Source: ATA (2004).

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