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Innovation in the pharmaceutical sector

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by:

Charles River Associates

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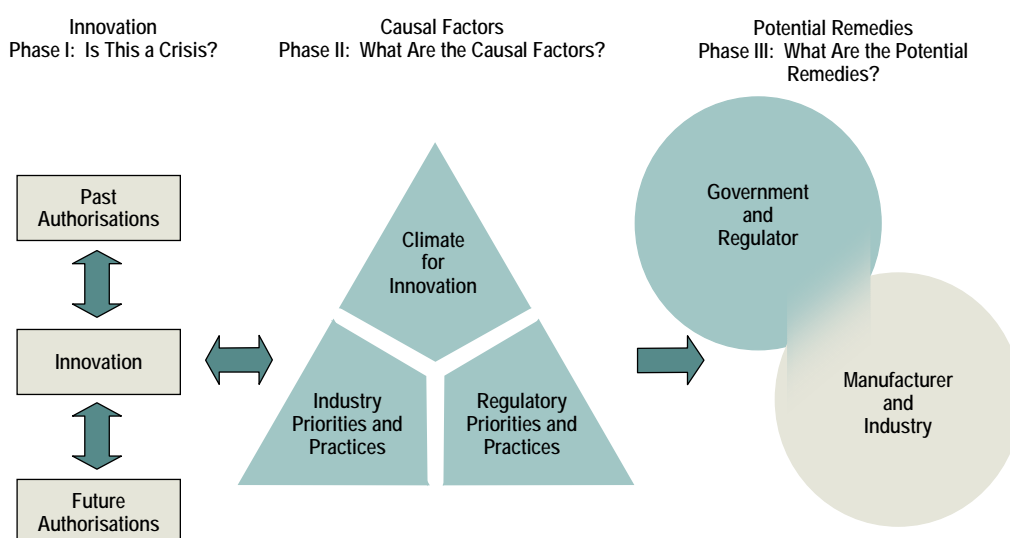
Executive Summary

Pharmaceutical innovation, as measured by the number of marketing authorisations applied for and granted, has fallen in the last several years. For example, both the EU and US regulatory authorities have recorded significant reductions in approvals from 1999 to 2003; from 27 to 17 in the EU (centralised procedure: new active substances, or NAS) and 35 to 21 in the US (based on new molecular entities, or NMEs).

Further, the European Agency for the Evaluation of Medicinal Products (EMA) and the US Food and Drug Administration (FDA) have noticed a reduction in the number of applications for marketing authorisations for new active substances, with the number of applications to the EMA falling from close to 40 in each of the two years 2000 and 2001 to 25 in 2002 and 34 in 2003.

Against this background, the Enterprise DG of the European Commission commissioned Charles River Associates to undertake a study investigating whether there is a worldwide crisis in innovation in the pharmaceutical sector (“Phase I”), the reasons behind this crisis (“Phase II”), and the tools available to kick-start innovation (“Phase III”). Figure 1 illustrates CRA’s approach to answering these questions.

Figure 1: The three phases of the project



Source: CRA, Invitation to Tender

Is there a worldwide crisis in innovation?

There has clearly been a significant reduction in applications and authorisations of new active substances in Europe, in the US and in Japan over the last three years. This has resulted in considerable concern in the regulatory community with significant contributions from the European Commission, the Food and Drug Administration in the US and the Japanese Ministry of Health, Labour and Welfare regarding how innovation could be encouraged.

However, putting the recent downturn into a historic perspective suggests that the current decline appears small relative to historic volatility. The recent history of applications (and the close relationship between applications and authorisations) suggests a recovery in authorisations is likely in 2004/2005. Therefore although this is concerning, we do not believe the recent decline reflects a crisis in innovation.

Indeed, based on an assessment of company pipelines we are able to look at the likely number of new active substances brought to market or at least applying for marketing authorisation over the next five years in Europe. Based on a prediction of how many products will move from phase to phase in the R&D process and enter the registration procedure, our forecast suggests that (unless there are dramatic changes in the probability of moving from one phase to another) there will be a gradual increase in marketing authorisations over the next couple of years. This supports our assessment that the recent downturn does not reflect a trend.

We have also assessed the degree to which new technologies offer the opportunity for future growth. Within our data we can identify many new technologies, such as gene therapy, and see that these contribute to the growth in products in early stages of development. However, we can only observe these products in any numbers in Phases I to II of clinical development. Given the time it takes to go through the whole development process, it is unlikely that these products will contribute a significant number of applications or authorisations over the next five years.

There is also, however, considerable concern regarding the types of product being developed. The experiences in Europe and the US seem to diverge in terms of biologics. In the US there is a higher proportion of new biologic products coming onto the market, while in Europe, although the assessment is made more complex by the interaction between the centralised and the mutual recognition procedure, this does not appear to be the case.

Equally, the introduction of an orphan drug designation process in Europe has led to an increasing proportion of marketing authorisation applications having this designation. Given the relative stability of number of drugs going through the US orphan drug designation process and given the downturn in applications, we believe it is likely that the share of European authorisations assigned as orphan drugs is likely to reach a level similar to that experienced in the US.

In terms of therapeutic value, we have not found a European source of data that allows us to make a meaningful comparison of this kind or country data that would yield meaningful results. Analysis based on data from the FDA suggests there may be a shift in the mix of products approved. In recent years the proportion of the total number of applications that results in new molecular entities appears to be somewhat lower and the number of products going through the priority channel has fallen as well. However, although this is one of the 'best' measures of therapeutic value available, it is by no means ideal. In particular, changes in the US regime make a like for like comparison difficult and it excludes the increasing number of biological drugs. Therefore, although there is a cause for concern, the jury is still out on whether the social value of new products is falling.

There is little evidence supporting the accusation that the industry is focusing only on blockbuster products or so called me-too products. Evidence from analyst reports suggests that there has been little change in the predicted distribution of peak sales over the last five years at a global level. This is in sharp contrast to the five years preceding this time period, which saw a concentration of effort on blockbuster products.

However, it is clear that global R&D expenditure over the past decade has shown a strong upward trend, which has continued in recent years. The 'crisis' therefore is that the number of new products has not increased whilst the overall level of resources being invested has risen dramatically. This appears to be both a long-term issue and one that is common globally.

There is also a clear trend with a higher proportion of R&D expenditure being spent in the US at the expense of Europe and Japan. However, even allowing for this, R&D expenditure in Europe has continued to grow significantly.

Causal factors determining the fall in innovative productivity

To examine the causal factors behind changes in innovative capacity, we distinguished between the following groups:

- Cost of developing new innovative drugs;
- Expected returns from innovation; and
- Industry restructuring.

THE COST OF DEVELOPING NEW INNOVATIVE DRUGS

Although it is possible to argue over the particular methodology used to measure costs, there is considerable evidence to show that the cost of researching and developing a pharmaceutical

product has increased. Over the last decade there has been a five-fold increase in the costs of clinical development and a 60% increase in the real costs of preclinical development.

These costs have been rising even though pharmaceutical companies have been concentrating on stopping investment on products that are unlikely to make it to market and have reduced overall time between synthesis and launching the product. There appears to be a number of contributing factors:

- There is clear evidence that the cost of research and development varies by therapeutic group and that the mean cost of undertaking clinical trials rises with the complexity of the product. Thus, one potential explanation of the cost increase is a shift to more complex products. However, it is less clear that the product areas that have seen the most significant growth over the last five years or where future growth is predicted are systematically more complex than those focused on in the past. Therefore, although this is likely to contribute to the rising costs, we see this as only part of the explanation.
- There is evidence that the number of trials required to support a new product has risen over the last ten years. This is thought to be due to a number of factors. In particular, the need to have comparative studies to support marketing, formulary negotiations and reimbursement decisions has increased.
- There is no compelling evidence that regulatory requirements associated to the authorisation process have been a major component in the long-term increase in costs, but they may have led to an increase in costs in the late 1990s, due to a number of high profile product withdrawals.
- Regarding new technology there is a general consensus that this has increased the costs of research and development in the short-term. There is less consensus regarding how quickly these costs will pay back and whether this will result in the cost of development falling back to the original level or lowering these costs dramatically.

We have also reviewed the implications of the changing costs of research and development for innovation within the EU. These implications are potentially alarming, as there appear to be two significant threats:

- A cost-based threat based on the lower research and development costs in lower income parts of the world.
- A loss of competitiveness compared to the US, even though there appears to be a cost advantage in undertaking trials in Europe.

Finally, we considered whether financing costs could have contributed to the decline in authorisations. Current authorisations of new medicinal products reflect research and development efforts of the past ten to fifteen years. Thus, any change now may reflect a lack of R&D spending in the past, a hypothesis put forward by the FDA. Our analysis confirms that in 1994 the growth rate in R&D investments dropped significantly and this may have caused some of the downturn we observe now. One factor explaining this drop is more

difficult financing conditions due to reduced investor confidence. However, it is difficult to identify a sharp change in expectations and investor confidence around this time and hence we do not attribute a significant weight to this effect.

EXPECTED RETURNS FROM INNOVATION

We do not believe that the falling long-term productivity of research and development is attributable to changes in returns to innovation; however, it may have a significant impact on the focus of innovative activity and the incentive to develop products in the future:

- **Price regulation and parallel trade:** Almost all European countries have introduced cost containment measures in the last few years, including price cuts and freezes for patented products. Given that these measures were implemented relatively recently, it is unlikely that they have had an effect on the current level of innovation. However, since they directly put downward pressure on industry profits and hence the returns to innovation, tougher price regulation and parallel imports are likely to reduce the incentives to innovate in the future.
- **Growing importance of generics:** Even countries that have not traditionally had a strong generics market, such as Spain and France, have recently introduced rules to encourage generic competition. The direct effect of stronger generic competition is that it reduces the expected revenues after patent expiry, leaving in the most extreme scenario only the patent period to earn any profits. Hence, the returns to innovation and the incentive to innovate are reduced. Given that many European countries have had strong generics markets for several years, e.g. the UK and Germany, it seems likely that this effect has already impacted on the level of innovation we currently observe. Strong generic competition is likely to have two secondary, longer-term effects. First, the increased importance of the branded period will provide an incentive to channel resources into R&D for new products that will gain acceptance quickly in order to keep a competitive product portfolio. On the other hand, it will increase the incentive to focus on incremental innovations that will lead to a further period of market exclusivity.
- **Therapeutic reference pricing:** By reducing the price premium that first products in a new category traditionally enjoy in many European countries, therapeutic reference pricing for patented products will reduce the returns to innovation and hence the incentives to invest in R&D. Since therapeutic reference pricing has only recently been introduced in some EU Member States, it is unlikely that it has already had an effect on the current level of innovation. In the longer term, by rewarding products that are not in a reference price group, therapeutic reference price systems could contribute to a more efficient allocation of R&D resources to truly innovative products, similar to the effect of cost-effectiveness studies described below. The impact on innovation therefore depends on the implementation of the policy.
- **Data protection and market exclusivity period:** Granting extended data protection and market exclusivity periods for significant new indications of already existing products or products for certain groups of patients, such as children, increases the returns to

innovation and hence the incentive to invest in R&D in such products. The European programme for orphan drugs was only recently introduced and the paediatric programme is still in preparation, so they cannot have affected the current level of innovation that we see today. However, they are likely to positively influence R&D in the future.

- **Cost-effectiveness measures:** Cost effectiveness studies could increase R&D costs by requiring the collection of additional data on products' pharmacoeconomic value. An increase in costs will clearly reduce the incentive to invest in innovate products. However, by providing incentives for pharmaceutical companies to invest in R&D for cost effective products with a true social benefit, cost effectiveness requirements are likely to increase the efficiency of R&D allocation. Cost effectiveness measures are increasingly being introduced by European countries and are therefore likely to affect the incentives to innovate in the future.
- **Location of R&D:** It is argued that companies have an incentive to invest more R&D resources in countries where the expected returns to innovation are higher (for example due to the marketing advantage of research being done by local Key Opinion Leaders (KOLs)). Given that cost containment measures in the European Union are increasingly putting pressure on returns to innovation, this may contribute to R&D increasingly moving to other markets, especially the US.

Our analysis of the empirical evidence related to the above-mentioned factors suggests that while prices of newly launched drugs are not increasing in Europe, the share of new drugs in total pharmaceutical expenditure is growing. In addition, population ageing and growth contribute to a situation in which pharmaceutical expenditure and hence the total pie available for pharmaceutical companies continues to increase. Market researchers expect the European pharmaceutical market to grow by an average of 5.2% per year between 2002 and 2007. In combination, these two factors – an ageing population and more new products in the product mix – are likely to positively affect the incentives to innovate in the future by increasing the potential returns to innovation that R&D pharmaceutical companies can obtain.

We find only limited evidence of the effectiveness of cost containment measures before the late 1990s and therefore these do not seem likely to have resulted in a reduced incentive to innovate. Hence, it seems unlikely that this was responsible for the fall in authorisations over the last few years. We assess that the factor that is having the greatest impact on expected revenue for new drugs is the increase in generic competition and this may be resulting in a diversion of effort to maintaining revenues. There is, however, a clear concern that encouraging more intense generic competition, without an increase in prices during the branded period will lower the returns to innovation in the future.

INDUSTRY RESTRUCTURING

Since the early 1990s the pharmaceutical industry has gone through a process of significant consolidation through mergers and acquisitions. While we have been writing this report,

another mega-deal is underway, the Sanofi-Aventis merger. A number of analysts have argued that this M&A activity may have harmed innovation. Indeed, when looking at the motives of many of the mergers we find that cost cutting was high up on the agenda. We find that four factors suggest a negative short-run effect on the number of pipeline products and research pipelines. We conclude that the short-run impact of any merger is likely to be negative. A systematic study of the effect of the pharmaceutical mergers on R&D expenditure confirms this view for smaller mergers.

Determining the long-run effect on R&D, however, is much more difficult. One important motive for the merger activity was the desire to improve the product portfolio and to address the expected drop in capacity utilisation and cash flow following the patent expiry of major drugs. Indeed, positive knowledge spill-over effects and economies of scale and scope may improve the productivity of innovative activity. Moreover, reducing the number of rivals thriving to win the “race” for an innovation (a patent) increases the chance of winning for the remaining innovators and may also increase the value of the innovation if later competition is reduced. These are arguments that suggest that merger activity may lead to improved long-run innovation.

There are, however, also potentially negative long-term effects on competition. If the combined entities gain a significant headway relative to their rival firms in certain research areas, this may put off rival firms’ efforts to innovate in this therapeutic class. Moreover, if a merger leads to the elimination of an independent line of research, the expected time until discovery may be increased raising the expected cost of R&D. Competition policy addresses these concerns and almost all large mergers in the pharmaceutical industry went along with divestitures or other remedies designed to address the potentially negative effect for patients.

Potential remedies

As described above, our study identified a range of factors that have played a part in the recent fall in applications and authorisations and the longer-term reduction in the productivity of innovation. In addition, there are overlapping factors that have resulted in a drift of innovative activity being undertaken in the US rather than in Europe (or Japan).

Based our analysis, we believe the very low level of authorisations observed in 2002 and 2003 were unusual and this does not in itself warrant particular intervention (given our focus on the next five years). Without any targeted regulatory remedies we would expect the number of new active substances to return to the level seen over the last ten years.

Instead, the focus should be on the longer-term global issues regarding the reduced productivity of innovation and the delay in the benefits arising from new technologies. There are also particular issues that relate to the location of innovative activity in Europe.

In formulating the priorities for kick starting innovation in Europe, it was important to take into account the changes that have already been made. In Europe we already have a large number of policy proposals to be implemented in the course of and beyond the review of the EU pharmaceutical legislation. These are likely to address a number of the key issues identified:

1. Faster market access for products offering significant therapeutic benefits through the accelerated procedure and the possibility of conditional approval for breakthrough treatments. ***This is likely to bring forward new products and increase the returns from truly innovative products although – given the wave of product that are still in Phase II – this will not have an immediate effect.***¹
2. Streamlining the regulatory process and changing the focus of the EMEA to the provision of scientific advice and support to industry – providing greater certainty and facilitating procedures for companies that need to seek advice regarding development issues in particular therapeutic and technology areas. ***This addresses one of the potential concerns regarding fragmentation of the European system.***
3. Greater clarity regarding the level of market exclusivity through a harmonised ten-year data exclusivity period (with an additional year granted for innovative research on already marketed products) while allowing generic applicants to prepare for the market before data exclusivity expires (known as the Bolar provision). ***This increases transparency and consistency across the mutual recognition and centralised procedure and may increase incentives to innovate for products that would otherwise have received a shorter period of exclusivity.***

However, given the long-term reduction in productivity more will need to be done. Based on our analysis of the nature of the problem we set out below the appropriate priorities for European policy over the next five years. This takes into account the many recommendations suggested by the FDA in the US, by the G10 Medicines Group and the European Commission in Europe, and the Ministry of Health, Labour and Welfare in Japan as well as by the industry itself to address the global and regional issues with regard to innovation in the pharmaceutical industry. The objective is to set out the range of recommendations and the priority that should be given to them to allow all stakeholders to focus on some selected areas and make the most efficient use of the limited resources for change and reform that are available. Our recommendations fall into three groups:

- Clearing the bottleneck of Phase III;
- Improving Europe's attractiveness as a location for innovative activity in the medium term;

¹ Note however that in exceptional circumstances, e.g. unmet medical need, the current regulatory framework allows for products to be authorised after phase II.

- Additional recommendations with lower priority.

CLEARING THE BOTTLENECK OF PHASE III

Based on the findings of our study there is currently a bottleneck in Phase III development. Hence, we believe that the most effective way to increase the number of marketing applications and authorisations will be to clear this bottleneck by helping companies accelerate the process of bringing these products to market. This can be done by focusing on two cost-related strategies:

1. The applied sciences require further development in order to catch up with development in basic research and new technologies. Policy needs to focus on the “critical path” between basic research and product development and in particular on activities such as the clinical trial designs and the development of appropriate biomarkers. Biomarkers are already used to inform development decisions in industry (e.g., for early clinical ‘proof of concept’). There is a progression and continuum from ‘biomarker’ (used as a development tool) to ‘surrogate end-point’ (sufficiently widely accepted to be used as the clinical basis of approval). ***This would appear to apply equally to Europe as to the US. Focusing on the development bottleneck would appear to represent high returns.***
2. Communication between the authorisation authorities and pharmaceutical companies during the development process should be improved. Examples could be an agreement on using advances in applied sciences as surrogate end-points for a particular product or developing a better understanding of the pro and cons of focusing a product’s development on a narrow area where products can be shown to be superior resulting in a quicker review process versus focusing on a wide range of therapies. In addition a more formal process would give the industry greater certainty and increase the efficiency of the development process. A number of dimensions have been identified regarding further improving the dialogue between industry and regulators during the development phase in Europe so as to reduce requests for additional data and regulatory questions following submission. ***There appears evidence that the more formal consultation process during Phase II conducted by the FDA in the US could be usefully applied to Europe. In an informal way, this is already recognised in the structural changes to the EMEA and may be particularly beneficial to new technologies and smaller companies.***

IMPROVING EUROPE'S ATTRACTIVENESS AS A LOCATION FOR INNOVATIVE ACTIVITY IN THE MEDIUM TERM

In addition to these strategies, there are some longer-term strategies that should also receive high priority in order to create a more favourable R&D climate and ensure Europe's competitiveness especially vis-à-vis the United States:

3. Identification of industry capacity and the main bottlenecks in the key development resources. The number of development projects in Europe may partly represent current capacity of research staff, management of clinical trials, and patients willing to participate in trials. *The EC should consider whether appropriate investment is being made in the long-term capacity of the European industry to maintain the level of clinical trials and steps needed to maintain Europe's cost advantage. This may involve working with Member States to communicate the need for public participation in drug development.*
4. The changing structure of prices. Encouraging generics while holding prices of branded products constant or even forcing them to fall reduces the returns to innovation. In the longer run this lowers the incentive to bring products to the market. If the incentive to innovate should be maintained, the encouragement of generics needs to be matched by an increased focus on price setting during the patented period. *By increasing the returns to innovation in Europe, this could also help in luring R&D back to Europe from the US.*
5. There is a recognition that more flexible pricing structures may be required in order to channel R&D investment to its most efficient and socially desirable use. For example, many claim that the market mechanism fails to operate in new drug evaluation. In particular, an accurate evaluation of innovation should allow prices of medicinal products to go up if the value of the innovation is considered to warrant this. Currently, there is usually no possibility for manufacturers to receive a price increase for a product that is already on the market. *The possibility to achieve a price increase for a particularly valuable product that is already on the market could encourage further research and development after the product is launched, this clearly interacts with policy on extending the period of protection, the latter of which has already been implemented.*
6. The effectiveness of R&D tax credits has often been questioned by academics. It was argued that R&D was very insensitive to tax credits and these largely influenced the location of R&D rather than the level of R&D. More recent academic work has suggested that R&D tax credits do work in terms of encouraging R&D and can be a useful tool for encouraging innovation. At the same time we are seeing a number of countries choosing to focus on targeted R&D tax credits to encourage investment in therapeutic categories that are seen as having too little investment. *There is an*

argument that co-ordination of tax credits is required at the European level if the spillover effects are to be fully taken into account.

7. Better co-operation is required between public and private research organisations carrying out basic research (i.e. between universities, research institutions and the pharmaceutical industry) in order to overcome fragmented research systems. In particular, the US National Institutes of Health (NIH) is seen as co-ordinating public and private research, bringing together funds, scientific knowledge and centres of excellence. At the European level, virtual institutes of health have been suggested to deal with this issue. ***This appears to already have been recognised as potentially beneficial, careful follow-up is recommended.***

ADDITIONAL RECOMMENDATIONS WITH LOWER PRIORITY

Finally, there are some recommendations that we believe may promote innovative activity, but the effects of which are more difficult to achieve and could also be ambiguous:

8. Fundamental changes to reimbursement systems. A reflection has been launched by the European Commission on possible other mechanisms to control health care spending, including possible free pricing by manufacturers of medicinal products in combination with national rebates or discounts based on the Member State. One of the underlying intentions is to reduce large price differentials within the EU. ***Although this might reduce leakage through parallel imports, it does not in itself change the returns to innovation. It may reduce costs for pharmaceutical companies if the pricing and reimbursement process is streamlined in the EU, but if the possibility of national rebates and discounts remains, it is likely that negotiation over price may become negotiation over discounts and that nothing fundamental will change.***
9. Vigilance over the competitive effects of mergers. Evidence to date does not support any loss in long-term innovative productivity resulting from the wave of mergers and acquisition during the 1990s. Indeed, this appears to have been driven by the reduction in new product opportunities rather than driving this. However, continued vigilance by competition authorities is required. ***There is no support for tougher merger policy based on our analysis, but continued vigilance is required.***
10. The incentive impact of therapeutic reference pricing needs to be considered with care. The effect of therapeutic referencing pricing on the incentives to innovate depends on how therapeutic groups are constructed, at what level reference prices are set and how so called “me-toos” are identified. In theory, the effect can be either to increase or to reduce the incentives to innovate. Therefore, it is crucial that – when setting up therapeutic reference pricing – the likely effect on innovation is taken into account. ***We have found relatively little published evidence of the impact on the incentives to innovate. However, therapeutic reference pricing is relatively new in***

Europe. We believe that further research is required on how the structure of the reference pricing system affects the incentive to innovate.

11. Development of a common methodology in the EU for the assessment of relative clinical and cost effectiveness. ***If realised at the European level, this will provide a useful benchmark for assessing the on-going quality of pharmaceutical innovation (in terms of therapeutic value of new products). The impact on innovation depends on the connection with the reimbursement system. If premiums for innovative products are allowed, it can improve innovation, but otherwise the effect is unclear.***
12. Improving access to venture capital in Europe has been identified as a substantial issue in Europe. Pharmaceutical innovation is a long-term risky investment. The lack of a European venture capital base, especially compared to the US, has long been identified as a problem. In addition, the role played by the NIH in the US offers a model to develop this on a European basis. ***While virtual centres of excellence may enhance the transfer of research information, complementing this by public funds might make the industry less risky and more attractive for private venture capital.***

CONCLUSIONS

There are already many plans to encourage innovation globally, within the European Union, and at the level of Member States. However, there is a clear danger in focusing on so many policy areas that efforts are too diffuse and lack of co-ordination prevents the true benefits from materialising.

In this report we have attempted to relate the size of the problem, the underlying causes and how these remedies meet up to the task at hand. We have identified seven recommendations where the European Commission, Member States and the industry should work together to improve the European environment for innovation:

- Focusing on how technical advances can improve the later stages of the development process (similar to the Critical Path debate in the US);
- Improved communication between regulator and industry during key phases of development;
- Addressing fundamentals to prevent future bottlenecks and increase industry capacity;
- Using branded prices to sustain incentives to innovate in the face of greater generic competition;
- Greater flexibility in pricing to reflect innovation in existing products;

- Co-ordinating R&D tax credits to maximise benefits to Europe; and
- Facilitating improved public-private co-operation in research in Europe.

These changes are necessary if Europe is to compete with the US and Japan as a location for innovative activity. These will also contribute to the global efforts needed to improve innovative productivity.

1 Introduction

Pharmaceutical innovation, as measured by the number of marketing authorisations applied for and granted, has fallen in the last several years. For example, both the EU and US regulatory authorities have recorded significant reductions in approvals from 1999 to 2003; from 27 to 17 in the EU (centralised procedure: new active substances, or NAS) and 35 to 21 in the US (based on new molecular entities, or NMEs).

Further, the European Agency for the Evaluation of Medicinal Products (EMA) and the US Food and Drug Administration (FDA) have noticed a reduction in the number of applications for marketing authorisations for new active substances, with the number of applications to the EMA falling from close to 40 in each of the two years 2000 and 2001 to 25 in 2002 and 34 in 2003.

More troublesome is that the number of yearly authorisations is not increasing despite increasing research and development (R&D) expenditures by pharmaceutical manufacturers. The decreased rate of applications and approvals coincided with R&D expenditures that grew by 111% (EU) to 184% (US) from 1992 to 2002 in nominal terms, similarly, major advances in biotechnology, including the mapping of the human genome, have not yet produced a visible effect on marketing authorisation applications. This would seem to point to a crisis in innovation.

On the other hand, volatility in marketing authorisations and applications is not a new phenomena; historically, authorisations fluctuate depending on economic, regulatory, and political circumstances. The question is, then, whether there is a crisis in innovation within the global pharmaceutical industry or whether the recent downturn is nothing more than a trough in the development cycle that will correct itself over time.

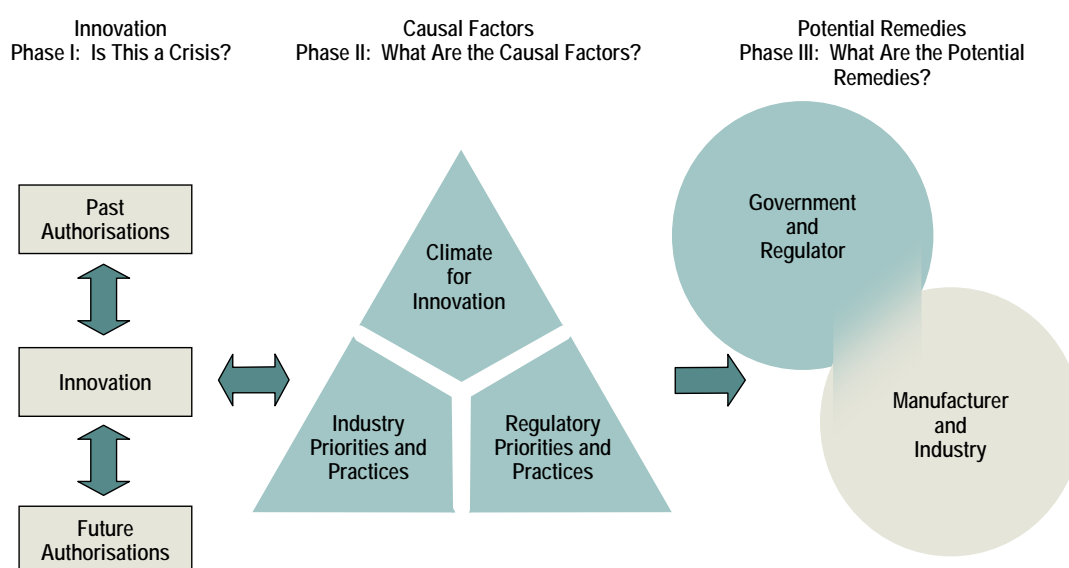
Against this background, the Enterprise DG has commissioned Charles River Associates to undertake a study investigating whether there is a worldwide crisis in innovation in the pharmaceutical sector (“Phase I”), the reasons behind this crisis (“Phase II”), and the tools available to kick-start innovation (“Phase III”).

1.1 A three stage approach

Figure 1 illustrates CRA’s approach to answering these questions. The first phase focused on the analysis of the historical authorisations and prepared a baseline forecast of future authorisations. In order to assess whether the observed reduction in marketing authorisations filed and granted reflects a true crisis of innovation in the pharmaceutical sector, we considered the current downturn in a more long-term historical context, parallels from the debate on-going in the US and the likelihood that new technologies will increase the number

of products getting authorised in the future. Based on the findings of this analysis, we prepared a forecast that takes into account the past development activity; manufacturer R&D pipelines; survival rates for therapies in various developmental stages; secondary research on innovation; and industry and analyst forecasts.

Figure 2: The three phases of the project



Source: CRA, Invitation to Tender

The second phase investigated the causal factors that explain the potential reduction in innovative activity. Figure 2 shows the main areas that we investigated. The output of this phase will be an assessment of each causal factor.

Based on the causal factors identified as the drivers of the current fall in the number of authorisations, we analysed the potential remedies that could be proposed to regulatory and governmental bodies. We investigated the implications for pharmaceutical and biotechnology companies and the industry as a whole.

1.1.1 PHASE I

The methodology for Phase I involves four steps each of which refers to a section in this report. First, we explain what we mean by innovation in European pharmaceuticals (Section 2). In this section we discuss alternative measures to capture innovation and define the European pharmaceuticals industry. Second, we analyse historical data on marketing

applications and authorisations (Section 3). Third, we compare a number of methodologies for forecasting future marketing applications and authorisations (Section 4). Finally, we assess the situation of pharmaceutical innovation and discuss whether it is appropriate to characterise the situation as a crisis (Section 5).

1.1.2 PHASE II

The methodology for Phase II involves two steps. First, we have set out the evidence based on a review of the existing literature on factors driving innovation. We have subdivided this into four stages focusing on costs issues (Section 7), regulatory and reimbursement issues (Section 8) and how the industry is restructuring, in particular focusing on merger and acquisition behaviour (Section 9). Finally, we have attempted to rank these factors into whether they have a significant or insignificant impact on changes in innovative behaviour (this is set out in Section 10).

The results of our Phase II analysis were tested at a roundtable with representatives of the industry and regulators, based on a facilitated discussion of each of these sections. The results of the roundtable are incorporated in our policy recommendations in Phase III of this study.

1.1.3 PHASE III

Phase III brings together all the elements of the project into a set of recommendations at the European level, for Member States and for the industry itself. Phase III draws on the analysis in Phase I and Phase II and on the analysis undertaken in other parts of the world (especially the US and Japan) into appropriate policy options. The roundtable with industry experts and regulators also provided a very valuable input into the policy assessment process. Although we have introduced a number of new recommendations, we also see this report as providing a timely assessment of the many policy proposals that are already included in the review of European pharmaceutical legislation and in the European Commission's response to the G10 recommendations.

2 What do we mean by innovation in European pharmaceuticals?

To undertake a review of this kind we need to be clear regarding the boundaries of investigation, in particular:

- What we regard as pharmaceuticals for the purposes of this project;
- What we define as innovation; and
- The boundaries of the European pharmaceutical industry.

2.1 A definition of pharmaceuticals

This project concerns the development of medicinal products for human consumption, this therefore includes new chemical drugs and biologics but excludes medical devices that may substitute for pharmaceutical products. Clearly, these distinctions are constantly being blurred by new technologies and we note how a number of new technologies illustrate this point.

2.2 A definition of innovation

Innovation can be defined as technological progress that leads to the creation of an entirely new product or a reduction in the cost of producing or an increase in the therapeutic value of an existing product.²

There are a number of alternative measures of innovation. These are useful to understand innovation from different perspectives and to prepare for Phase II, our analysis of the drivers of innovative activity. In the following we discuss a number of these measures and how they are useful:

Product versus process: It follows from the above definition of innovation that innovative activity can affect the production process (process innovation), can lead to a new product or change the quality of a product in terms of therapeutic value (product innovation). In practice, it is often difficult to distinguish product and process innovation. Product innovations that are based on new chemical substances often require new processes. Generally new drugs are

² Note that the literature on innovation economics sometimes distinguishes inventions (creation or finding of a new idea, product or process), innovations (an invention that has been implemented/marketed) and diffusion (the distribution to the mass market).

developed using the conversion of natural substances or chemical synthesis. Since most new drugs require the use of a particular conversion or synthesis, the development of new drugs is often accompanied by the development of new chemical processes. In most of the following analysis we will therefore *focus on product innovation*.

Dimensions of product innovation: Medicinal products have a number of quality dimensions. It is common to distinguish the efficacy, the safety and the convenience of a medicinal product. Innovations can lead to new active substances, new indications for existing products or new ways of administering the same product. All three types of innovation can, in principle, be of significant value to patients. Mainly due to data limitations we *focus on the development of medicinal products that are based on new active substances but where possible we consider measures capturing the broader definition*.

Fundamental vs. applied research: Some innovation can have direct implications for new products while other innovation may come out of fundamental research, trigger new innovations and pay off only in the distant future. This distinction is important as some theories of innovative activities suggest that innovative activity depends on revolutionary findings in fundamental research, which then lead to a wave of new more applied innovations based on these findings. If this was correct we would expect to observe “revolutionary cycles”. We *discuss major technological advancements in the pipeline in Section 4.3 and address the theory of innovation cycles more extensively in Phase II*.

Value of the innovation: The therapeutic advancement of a medicinal product determines the value of a product innovation to patients. However, despite various suggestions and demands³ there exists no harmonised definitions of new medicines with an added therapeutic value (compared to existing products) on a European level.

There are a number of difficulties associated with the concept of therapeutic advancement:

- The added value of a new product may depend on the medical practice and culture in a specific region or Member State.
- An index of added value would have to compare the value of improvements that many people hesitate to value explicitly. Assigning weights to the value of an increase in life expectancy as opposed to an improvement in the side effects profile is clearly a difficult task.

To see the difficulty of a concept of therapeutic value, consider the following examples:

- Importance of therapy: The severity of an illness will affect the value of an innovation. A drug that provides new treatment for cancer is of higher priority than a drug that improves therapy of baldness. While it is simple to agree on extreme examples, determination of the priority of treatments often is a very difficult task.

³ See for instance the report of the Working Group on “Pharmaceuticals and Public Health” of the High Level Committee on Health from the 28th of March 2000 or the proposal of a Medicines Information Network for Europe (MINE) by the EMEA.

- Degree of improvement: Improvements may be in the area of quality, efficacy, or safety of a drug, affecting the added value to patients. Some new chemical entities are similar but not identical in molecular structure and mechanism of action to a pioneer new chemical entity. Arguably, these me-too drugs may be of lesser therapeutic value to patients than pioneering new drugs, however, the differences might be of significant value to patients.
- Number of people affected: Some illnesses affect only a small number of people. Together with the severity, the number of people affected will influence the value of a therapy, when considered at a population level.

A first step could be to assign the therapeutic advancement of a new product to one of a number of categories, e.g. new treatment for previously untreatable condition, significant extension in life expectancy, significant reduction in disability, significant improvement in side effect profile, significant improvement in ease of administration.⁴

Despite the obvious difficulties with a classification of therapeutic advancements, a number of classification systems exist on a national basis. The National Medicines Information Centre in Ireland, the Medicinal Products Agency Information Program in Sweden and the Transparency Commission in France are examples of national efforts to provide information on the therapeutic value of medicinal products.⁵ Unfortunately, none of these European systems lends itself to a long-run time series analysis that would allow us to examine the development of new drugs of significant added therapeutic value. We will however, *provide particular evidence for the number of products approved under the priority procedure with the FDA in the US*. This provides at least a rough, but imperfect, measure of how the expected therapeutic value added of products seeking approval and being approved is changing over time.

An alternative would be to look at market value as a proxy for therapeutic value. While it is likely that in many cases the added therapeutic value of a new drug is related to the commercial value, this need not be the case. DiMasi (2000) lists the following reasons: First, most classifications of therapeutic value do not take into account the number of patients affected.⁶ Second, there is some evidence that clinical development costs of drugs that receive a higher FDA therapeutic rating are higher. Third, approval success rates may differ across drugs, so products that truly offer significant therapeutic advancements may not prove commercially successful due to failings in the marketing of the product. Thus, although we recognise this is an imperfect measure, *we also consider the market value of new drugs*. The main publicly available source of information on market value is analyst.

⁴ See the report of the Working Group on “Pharmaceuticals and Public Health” of the High Level Committee on Health from the 28th of March 2000.

⁵ Indeed, in many countries products are assessed against a benchmark of cost effectiveness that implicitly values these dimensions but the products themselves are not assigned a value if they exceed the benchmark. For example, NICE in the UK.

⁶ If the number of patients is small, the medicinal products may be categorised as orphan drugs. The sales of the majority of orphan drugs are relatively small.

Effort/input vs. output: Innovative activity can be measured at various stages in the vertical production chain. Companies invest in R&D in order to develop new products (“R&D expenditure”). The first observable sign of outputs of research may be the application for a new patent attempting to protect the intellectual capital created by the innovative process. New active substances may enter phase I clinical trials and further phases of product development. Those substances that survive these states will be subject to an application for marketing authorisation and, if authorised, will be ready to be marketed (although even at this stage products may not be marketed). We can therefore look at various measures on this input-throughput-output dimension and study research productivity. *In particular, we compare the trends in R&D expenditure with the trend in new products, the ratio of products in different stages of development and the ratio between products in development to applications and authorisations.*

2.3 A definition of the European pharmaceutical industry

The European Commission’s Enterprise Directorate-General is not only interested in the level of innovation that is created to the benefit of European consumers – as proxied by the development of new products - but also aims at promoting innovation of European enterprises. We therefore also considered measuring the innovative activity of the European pharmaceutical industry.

Clearly, in the context of globalisation there exists no simple measure of the European pharmaceutical industry. A firm’s headquarters may reflect a tax decision or obsolete historical factors but not where innovative activity happens. Ownership is difficult to track with institutional shareholders that bundle the interests of large numbers of international investors or where firms have multiple share listings. Employees of multinational organisations are spread across many countries. Each of the different measures captures different effects on European citizens: tax, employment, knowledge spill-overs, dividends, capital gains etc.

As a practical matter we *track the innovative activity with regard to the location of the headquarters of the company involved in the development of the product.* However, in Phase II of this report we will also provide a *qualitative discussion of the location of the R&D activity of pharmaceutical companies.* This is particularly relevant given the ongoing trend to move research laboratories to the United States.

3 Phase I: Measures of innovative activity

To research recent trends in innovation we have quantified the number of applications and marketing authorisations over the past five years. These data have been collected for the EU, the US and Japan; collecting information from the three largest pharmaceutical marketplaces provides a good overview of global pharmaceutical innovation. The US, European and Japanese markets account for 90% of sales of new medicines launched during the period 1997-2001⁷ and 98% of new chemical or biological entities that were launched in the period 1998 to 2002 originated from pharmaceutical firms with a mother company in one of the three regions.

As well as providing a global perspective on innovation, we are interested in whether the pace of innovation in European pharmaceutical is the same as other countries, i.e. whether observable changes in innovation represent a global or European phenomena. This will help us determine whether causal factors in Phase II are impacting on the decision to apply and success rate of applications in Europe or whether any causal factors are affecting each region equally.

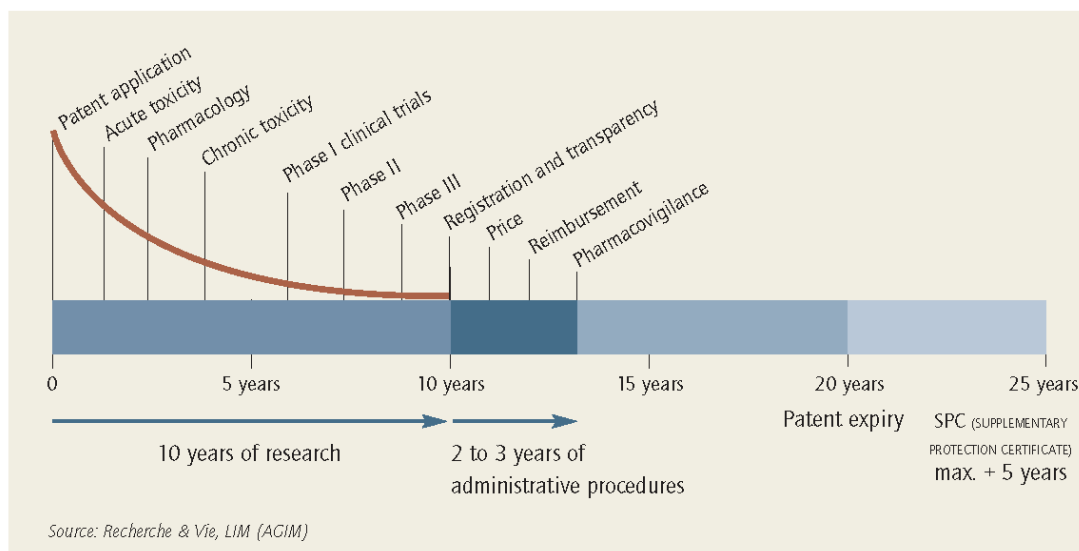
The main part of our analysis is based on data available from the EMEA for the EU and the FDA for the US. For each of these markets, the number of authorisations has been decomposed into relevant categories as permitted by the data. In addition, we collected data on the subsequent commercialisation of those products from the IMS data acquired for this study.

Before looking at our analysis of applications, authorisation and launches, we consider the inputs to the R&D process starting with total R&D expenditure and then evidence of today's innovative activity by examining products in company pipelines. This analysis exploits data from IMS R&D Focus.⁸

⁷ Source: IMS Health (MIDAS), Sept 2001. Cited in EFPIA (2003).

⁸ Although there are a number of commercial providers of R&D pipeline data, we have chosen to use IMS R&D focus. Each of these data sources has their own advantages and disadvantages. These data provide global information of drugs in development, monitoring the stage of the development, authorisation, and commercialisation.

Figure 3: Route of a new substance from discovery to patient access



Source: EFPIA: Medicines for Mankind

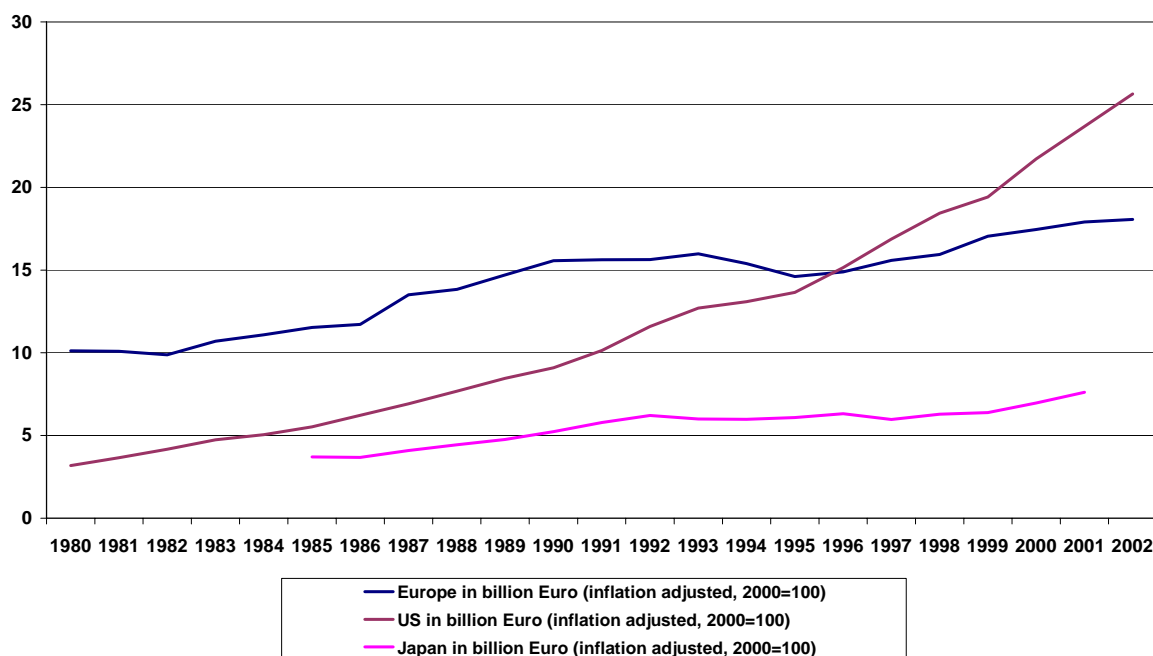
Figure 3 shows the main stages in developing a conventional medicine, taking on average 12 years from a scientific discovery to a new approved medicine. Patents are at the beginning of this process and investigation of the number of patents and patent citations could therefore be valuable as a guide for the long-term. Given the emphasis on the previous five years and the five years to come, our primary focus is on products already in phase I development.⁹

3.1 R&D expenditure

R&D expenditure provides a measure of the financial input to innovative activity. It is a broad measure as it captures effort that may lead to process innovation, fundamental new findings, new products or improvement of existing products. Figure 4 shows the increase in R&D expenditure in Japan, the US, and Europe in real terms.

⁹ For an analysis of patents see Gambardella, Orsenigo, and Pammoli (2000).

Figure 4: Pharmaceutical R&D expenditure 1980 to 2003 in billion Euro (adjusted for inflation, 2000=100)



Source: Parexel's Pharmaceutical R&D Statistical Sourcebook 2003/2004, pages 1, 289, and 296. European data based on official figures provided by EFPIA member associations. It covers all R&D spending within EFPIA countries (EU-15, excl. Lux, plus Switzerland and Norway) by national and foreign companies. The 2002 figure is an estimate. Japanese data from the JPMA Data Book 2003. US pharmaceutical spending is based on the PhRMA Annual Survey, 2003. Inflation adjustment and conversion to Euro using CPI data and exchange rates from Datastream.

As can be seen, there has been a significant increase in the total level of R&D expenditure, with the total level of expenditure increasing by about 56% in the last decade (1991 to 2001) in real terms. However, it is also striking that the share of expenditure undertaken in the US has grown from 32% to 48% in that period. Clearly, R&D expenditure in Europe has grown far less than in the US in real terms and even fell during the mid-1990s. Interestingly, the difference between the US and Europe is much more significant when looking at real R&D spending than when looking at nominal data, which many people commonly do. The development in Japan is similar to Europe in the sense that real R&D spending has grown much more slowly than in the US.

Evidence on the changing composition of expenditure of R&D is relatively sparse. A survey by CMR of expenditure in 2001 by a group of pharmaceutical companies showed evidence that expenditure on drug discovery had grown substantially faster than expenditure of clinical development, and this had grown significantly faster than non-clinical development.¹⁰

¹⁰ CMR International Institute for Regulatory Science (March 2003).

In order to identify the causes of a change in innovative activity it is helpful to study the change in the level of input and whether there is any change in R&D productivity. We turn to this in the next section.

3.2 New drugs being investigated

To look at the outputs of R&D expenditure we can look at new products in the pipeline prior to their application for authorisation at a number of different stages:

- Drugs in pre-clinical testing;
- Investigational new drugs applying to undertake clinical trials; and
- Drugs in different stages of clinical development from Phase I to Phase III.¹¹

3.2.1 PRECLINICAL

Looking at products in preclinical development, as set out in Table 1 below, we find there has been a significant increase of the drugs in preclinical testing in the last five years, with an average growth of 5% per annum. However, this reflects a rapid acceleration in the last two years, with growth rates of around 10%.

Table 1: Drugs in preclinical testing¹²

Stage	1999	2000	2001	2002	2003
Preclinical (Europe)	1284	1448	1582	1828	2228
Preclinical (world-wide)	3053	2986	3035	3295	3664

Source: IMS R&D Focus and PharmaProjects

According to R&D Focus the number of products in preclinical testing in Europe has grown considerably faster still.

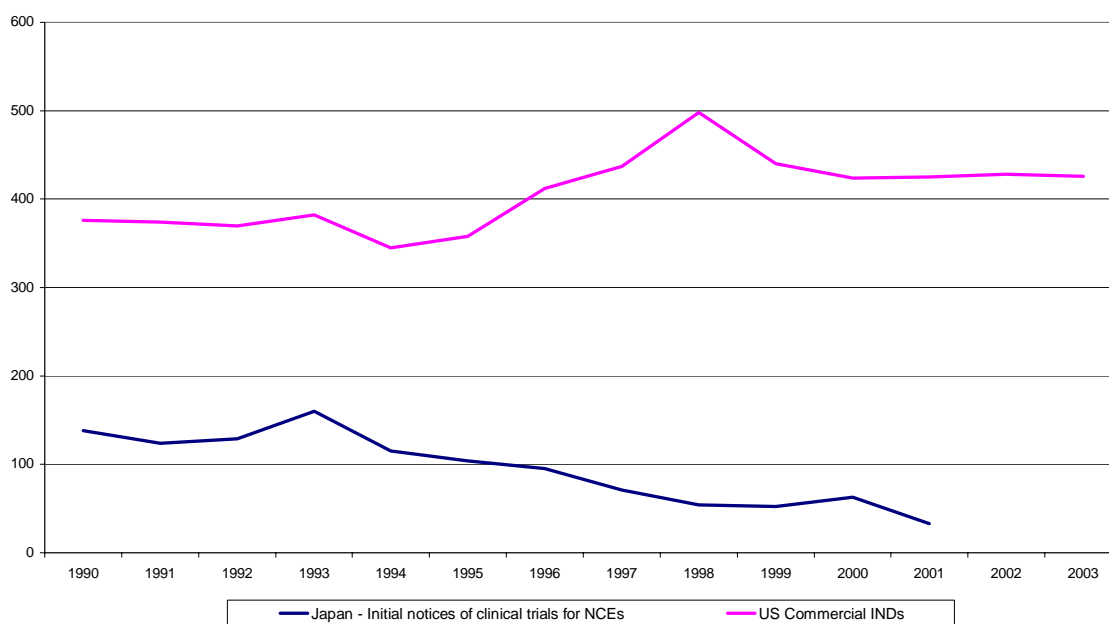
Taken at face value, this would appear to present a return to the increased resources being invested into research and development activities.

¹¹ Our primary focus is on understanding the process by which new products are developed and brought to market. We are therefore not interested in post-marketing trials and have not analysed Phase IV trials.

¹² The increasing in the number of products in preclinical can at least partly be explained by increased coverage of data providers. However, there does not appear to be a method for controlling for this.

In the US and Japan we are able to observe when drug companies apply to take these products into clinical development. However, this shows the growth in preclinical testing is not resulting in consistent growth in the number of new investigational drugs being taken into clinical development (as set out in Figure 5).

Figure 5: Investigational new drugs in clinical development in the US and Japan



Source: US data available from the FDA website. This data include all applications for investigational new drugs excluding biologics. For Japan, we have used data published in Parexel's Pharmaceutical R&D Statistical Sourcebook 2003/2004, pages 296. This data cover all applications for NCEs and are sourced to JPMA data book 2003.

On the basis of evidence from US, the number of new products going into clinical development is higher than it was in the early 1990s. However, recent growth has been disappointing. Compared to the US however, Japan has seen a significant reduction in the number of new investigational drugs.

The Japanese Ministry of Health, Labour and Welfare is aware of the falling number of clinical trials in Japan and attributes this to three main reasons: trials in Japan take longer, are of poorer quality and are costlier than in Europe and the US. Further, clinical trials in Japan are hampered by differences between the Western and the Japanese medical environment and customs and because, compared to the US, the environment for clinical trials in Japan is characterised by the following:

- A lack of incentives for patients to participate in trials due to low penetration of the significance of clinical trials and the fact that no financial incentives are offered;
- A lack of incentives for researchers to conduct trials, due to a low level of scientific evaluation and a lack of financial incentives; and

- A weak infrastructure for clinical trials with only few institutions equipped to conduct them and inadequate training of physicians and other staff.¹³

3.2.2 PRODUCTS IN CLINICAL DEVELOPMENT

In Europe, we do not (currently) have a centralised system capturing applications for undertaking clinical trials. However, using the IMS data we are able to consider products at different stages of development as shown in Table 2 below. We set out the number of new products by phase of development being undertaken in Europe.

Table 2: Products by stage in development in Europe

Stage	1999	2000	2001	2002	2003
Phase I	353	394	417	404	439
Phase II	461	492	545	604	663
Phase III	203	209	201	214	218
Pre-registration	94	91	88	69	73
Registered	33	43	40	43	34

Source: IMS R&D Focus

To undertake this search we have constrained it to products in development in one of the European Union countries and based the analysis on the latest phase of development. Even from this simple analysis it is possible to derive a number of observations:

- Although the overall growth of the number of products that are in clinical development each year is similar to the growth in products that are in preclinical development over our five-year period, this is heavily biased to the early stages of development. We have not (yet) seen an acceleration in growth rates as observed in drugs in pre-clinical testing;
- The growth in number of products in Phase II (at almost 10%) has considerably higher than the number of products in Phase I (at 5%) and Phase III (at less than 2%); and
- There has been positive growth in all phases of development but the number of products leaving developments and going into pre-registration and registration has fallen (pre-registration) or stayed the same.

Therefore the picture, based on products in development, is mixed. We are seeing growth in products in preclinical testing and this is starting to feed through into the early stages of clinical development. However, there is little evidence that the number of products close to launch (i.e. Phase III) is increasing. In clinical development therefore we appear to be observing a bottleneck with Phase II growing considerably faster than Phase I or Phase III.

¹³ Ministry of Health, Labour and Welfare of Japan (2002), pp. 18-19.

3.3 New drug applications and approvals

Concern regarding innovation in the pharmaceutical industry has arisen due to a fall in the number of marketing authorisation applications and approvals. It is therefore important that we understand the process generating these data and how to compare them across countries. In particular, we have focused on trying to collect data that allow us to compare like with like. There are many pitfalls to make in comparisons of this kind, in particular, we wished to make sure wherever possible that we were:

- Comparing the same measure of innovation: for example, comparing entirely new products with line extensions would be misleading;
- Capturing the entire picture: for example comparing approvals via the FDA with only EMEA data (omitting the mutual recognition procedure) is potentially misleading;
- Using the same definition regarding types of product: for example we need to be careful to allow for whether the FDA data include biologics or not when comparing to EMEA data.¹⁴

3.3.1 EU – CENTRALISED VERSUS MUTUAL RECOGNITION PROCEDURE

Medicinal products marketed in the European Union require a marketing authorisation. Marketing authorisations can be granted either via the EMEA¹⁵ or national authorities of the Member States. The European system offers two routes for authorising medicinal products. Under the “centralised” procedure applications are made directly to the EMEA, leading to the granting of a European marketing authorisation by the European Commission. The use of this procedure is compulsory for products derived from biotechnology, and optional for other innovative medicinal products. Alternatively, firms can apply for a national marketing authorisation in a Member State of their choice and the procedure operates by mutual recognition of national marketing authorisation. Purely national authorisations are available for medicinal products to be marketed in one Member State.

In practice, the EMEA is responsible for evaluating and the European Commission is responsible for the actual granting of marketing authorisations for:

- Medicinal products developed by means of one of the biotechnological processes referred to in Regulation (EEC) No. 2309/93, Annex, Part A (centralised procedure required).
- Innovative medicinal products referred to in Regulation (EEC) No. 2309/93, Annex, Part B, for which the applicant has voluntarily chosen the centralised procedure.

¹⁴ Surprisingly many comparisons are not made taking into account these factors.

¹⁵ It is the European Commission who officially grants the market authorisation, but based on the product evaluation undertaken by the EMEA.

- Medicinal products for which Member States have taken divergent decisions (Community referral in accordance with Article 30 of Directive 2001/83/EC).
- In cases of Community interest (Community referral in accordance with Article 31 of Directive 2001/83/EC).
- Medicinal products that are subject to a mutual recognition procedure and that may cause a risk to public health (Community referral in accordance with Article 29 of Directive 2001/83/EC).

National authorisations are granted by the competent authorities of the Member States for all medicinal products, which are not subject to Community authorisation. Once a national marketing authorisation has been granted, the applicant may submit the application in other Member States, requesting them to mutually recognise the marketing authorisation already granted.¹⁶

Development of applications and authorisations considered

In order to focus on innovative medicinal products, we collected data on the number of annual marketing authorisations for new active substances in medicinal products for human use that were granted by the European Commission and the number of finalised procedures for initial applications for new active substances for those products that went through the Mutual Recognition Procedure covering the time period 1998-2003.¹⁷ In order to get a timelier picture we also considered *applications for* marketing authorisations.

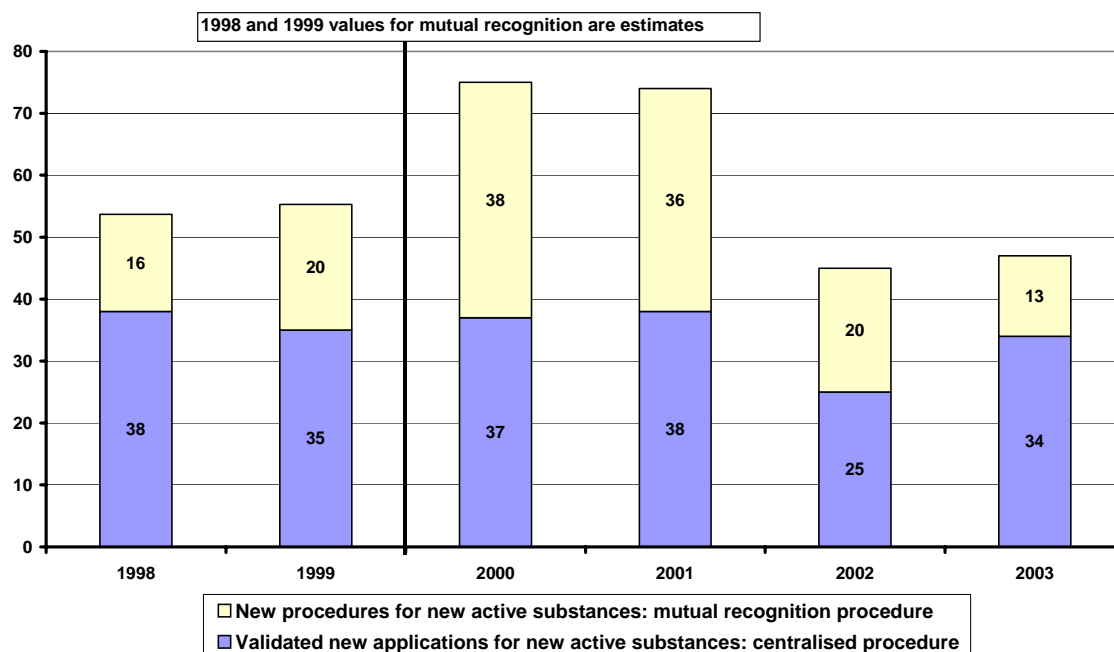
Figure 6 shows the number of validated applications and new procedures for marketing authorisations that refer to new active substances submitted under the centralised and the mutual recognition procedure. Note that there may be several applications or procedures for one new active substance recorded in the official data provided by the EMEA and the MRFG. We have eliminated repeat use procedures and multiple applications from the MRFG database and EMEA applications that refer to a new active substance for which an application has been made previously. As a result we focus exclusively on *initial* applications for new active substances.¹⁸

¹⁶ For those medicinal products where a national authority has already granted a marketing authorisation, there may not be an independent second national procedure in another Member State. There are two exceptions: medicinal products with a well established use and line extensions of authorised medicinal products for which no a priori harmonisation has been achieved.

¹⁷ A number of alternative measures of applications were considered. These are described in Appendix I.

¹⁸ For the centralised procedure, we “cleaned” the data received from the EMEA by excluding applications for all INNs for which an application had already been filed earlier, irrespective of changes in indication, company etc. For ongoing applications and applications that were withdrawn prior to an CPMP opinion, the EMEA was not able to provide us with information about the INN of each product and we used indications as a proxy for INN, excluding all repeat applications that relate to an indication for which a product had already applied for. In most cases, indications of the excluded applications were identical to earlier applications. In some cases, we also excluded applications that were filed with an indication very similar to an earlier application (e.g. “growth hormone”, “growth retardation in children” and “treatment of

Figure 6: Applications for new active substances in the EU under the centralised and the mutual recognition procedure* – 1998 to 2003



* New applications refer to the number of validated applications, which involve new active substances not subject to a previous application. Since several applications may refer to the same active substance the simple count of new applications per year may be higher. New procedures for new active substances refer to the first procedure started for this substance. Repeat use or multiple applications procedures are not counted.

Sources:

Centralised procedure: EMEA

Mutual recognition procedure: Based on EMEA data and reports provided on <http://heads.medagencies.org/index.html>. 1998 and 1999 figures are estimates based on the assumption that 65% of total new NAS applications (24 in 1998 and 31 in 1999) were initial applications (average share of initial NAS applications in 2000, 2001 and 2003; 2002 excluded due to unavailability of November data).

The data show a significant drop in the total number of applications from 74 applications in the year 2001 to 45 in 2002 and then a very slight recovery to 47 applications in 2003. It is interesting to note that while the fall in 2002 seems to reflect a one-time event if one considers the applications under the centralised procedure in isolation, the applications for new mutual recognition procedures continue to show a downward trend since the year 2000 (one cannot eliminate repeat use and multiple applications for the same active substances from the mutual recognition data for the years 1998 and 1999).

It is helpful to consider applications under the centralised procedure and the mutual recognition procedure jointly as firms have a choice to authorise Part B products under either procedure. Thus, the increase in centralised applications may simply reflect that more and more applications for List B products are filed under the centralised rather than under the

growth failure”). It should be noted that our application data obtained from this cleaning process is very close to the number of applications for new active substances reported by the EMEA in its Annual Reports.

mutual recognition procedure. We investigate this issue further below and find some support for this conjecture. However, when interpreting the data it is important to note that the two applications occur at different stages in the product development process. While the mutual recognition procedure is usually started *after* the first authorisation by a Member State with the submission to the next Member State, the date of an initial application for new active substances under the centralised procedure always reflects the first application in the EU. Thus, while we already observe a recovery of the number of applications under the centralised procedure, the same recovery may be underway regarding the number of applications under the mutual recognition procedure, but not yet visible in the data.

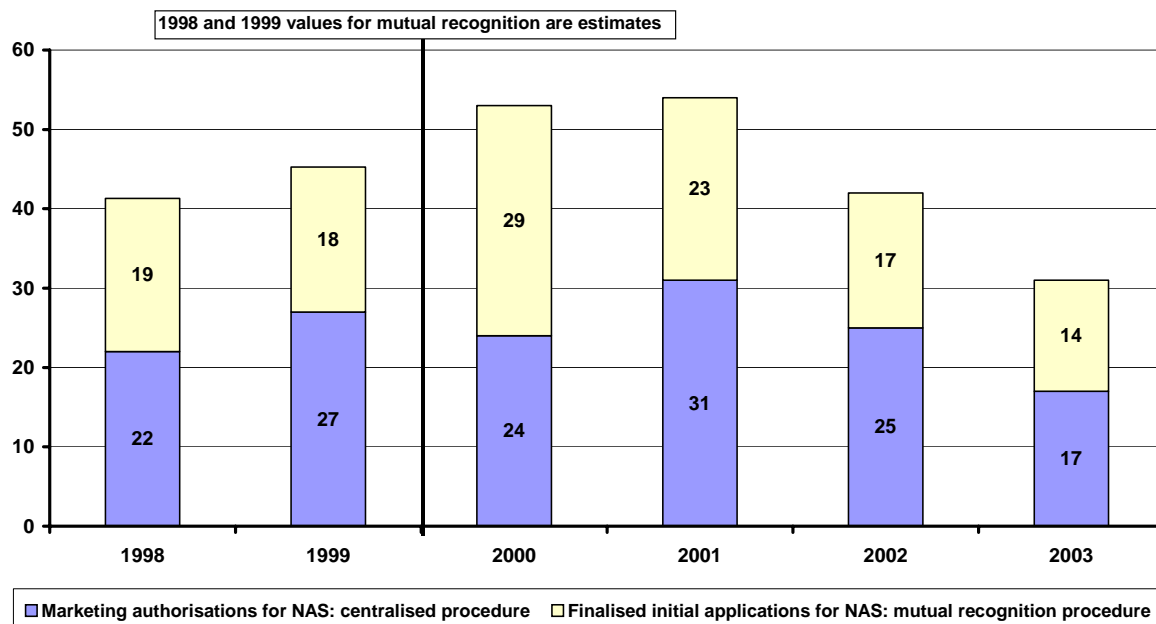
Figure 7 below shows how the lower number of applications leads to a lower number of authorisations. The figure shows the number of marketing authorisations for new active substances granted by the European Commission under the centralised procedure (by date of decision) and the number of finalised mutual recognition procedures for new active substances.¹⁹ We have used the same approach as for the applications in order to eliminate “double counting”: We have eliminated repeat use procedures and multiple applications from the MRFG database and only considered authorisations granted under the centralised procedure for new active substances for which no authorisation has been granted previously.²⁰

Figure 7 shows that the number of approved new active substances (excluding double counting) has fallen from 54 in 2001 to 42 in 2002 and 31 in 2003.

¹⁹ If an application has been referred to the EMEA, the procedure will be counted as finalised once the European Commission adopted a positive decision based on the CPMP opinion. Note however that there is always a time lag between the CPMP opinion and the final marketing authorisation decision by the European Commission.

²⁰ The EMEA Annual Reports do not provide the number of authorisations for new active substances, but only the number of positive opinions on medicinal products per year. Obviously, the number of authorisations for NAS should be lower than the number of positive CPMP opinions on products, and this indeed is the result of our data cleaning process. While the number of authorisations we find is close to the number of CPMP opinions published by the EMEA in 1999 and 2001, it is much lower in 2000 and 2002, suggesting that the share of multiple applications for the same active substance, e.g. under different brand names, was higher in the latter two years. It should also be noted that there is usually a time lag between the date of the CPMP opinion and the European Commission’s official marketing authorisation decision, which makes a comparison of “number of authorisations for new active substances per year” and “positive CPMP opinions on medicinal products per year” difficult.

Figure 7: Marketing authorisations and finalised applications for new active substances under the centralised and mutual recognition procedures



Source: Centralised procedure: EMEA. Mutual recognition procedure: Based on EMEA data and reports provided on <http://heads.medagencies.org/index.html>; 1998 and 1999 figures are estimates assuming that finalised initial applications are 52% of total finalised applications for NAS (37 in 1998 and 35 in 1995; 52% is the average relationship of initial and total new NAS applications in 2000-2003).

Again, it is important to note the difference in timing of the centralised and the mutual recognition procedures. Under the mutual recognition procedure the reference Member State adopts a first recognition and produces an assessment report within 210 days after the application to the reference Member State. Other Member States, which have also received an application (the so called concerned Member States) then have a maximum of 90 days to respond to the request for recognition of the decision of the reference Member State so that the procedure can either be finalised or referred to the scientific committee at the EMEA for arbitration. Under the centralised procedure the opinion of the CPMP is published in less than 210 days after the validation of the application and a decision is then taken around 90 days thereafter.

Table 3: Withdrawals and negative CPMP opinion as percentage of EMEA ended procedures²¹

	1998	1999	2000	2001	2002	2003	Total
Marketing authorisations (Parts A and B; products, not substances)	37	30	33	43	40	21	204
Withdrawn	19	8	11	11	13	4	66
Negative CPMP opinion	3	1	0	1	0	2	7
Total "failure" rate	37%	23%	25%	22%	25%	22%	26%

Source: EMEA press releases, CRA calculations

Table 3 confirms for the centralised procedure that the drop in the number of marketing authorisations for new active substances is due to fewer applications rather than a higher number of withdrawals or negative opinions by the CPMP. The data show that the “failure” rate is in the range of 22% to 26% in the period 1999 to 2003. The year 1998 is an outlier with a failure rate of 37%.

Note that withdrawals under the mutual recognition procedure almost never affect new procedures for new active substances, as these have already been authorised in one member state.

By applying the average failure rate of the past five years of 24% to the centralised procedure applications in 2003 we can gather a rough estimate of the authorisations under the centralised procedure expected for 2004. Adding the number of applications under the mutual recognition procedure then yields the expected total number of authorisations for 2004. These calculations suggest that the total number of authorisations may go up from 31 in 2003 to 39 in 2004. Note that this is only a very rough estimate as new applications are filed and decided in 2004.

Thus, without considering the analysis of the new active substances in the pipeline (see Section 4.2) we would therefore expect the number of authorisations to increase in 2004 after falling two years in a row since 2001.

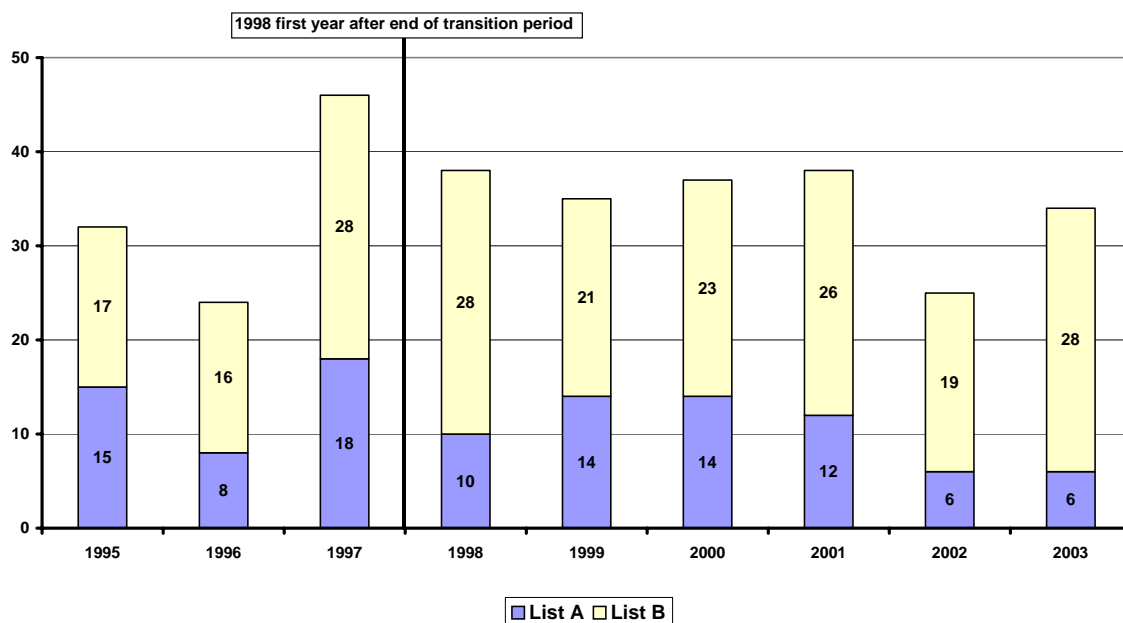
We now turn to a more detailed analysis of the applications and authorisations by new active substance.

Figure 8 shows the number of initial marketing authorisation applications under the centralised procedure for Part A and Part B products separately. The data show that after falling in two consecutive years, the number of Part A applications remained the same in 2003 as in 2002 while the applications for Part B products went up. This observation is

²¹ Note that the data in Table 3 refers to products and not to substances. Thus, using this failure rate for initial applications for new active substances implies the assumption that the ratio does not differ between products and substances.

consistent with the conjecture that part of the increase in the observed applications under the centralised procedure may be due to a higher preference to that procedure relative to the mutual recognition procedure, where the number of products dropped.

Figure 8: Number of initial marketing authorisation applications under the centralised procedure: List A vs. List B (by validation date, counted by INN or indication)

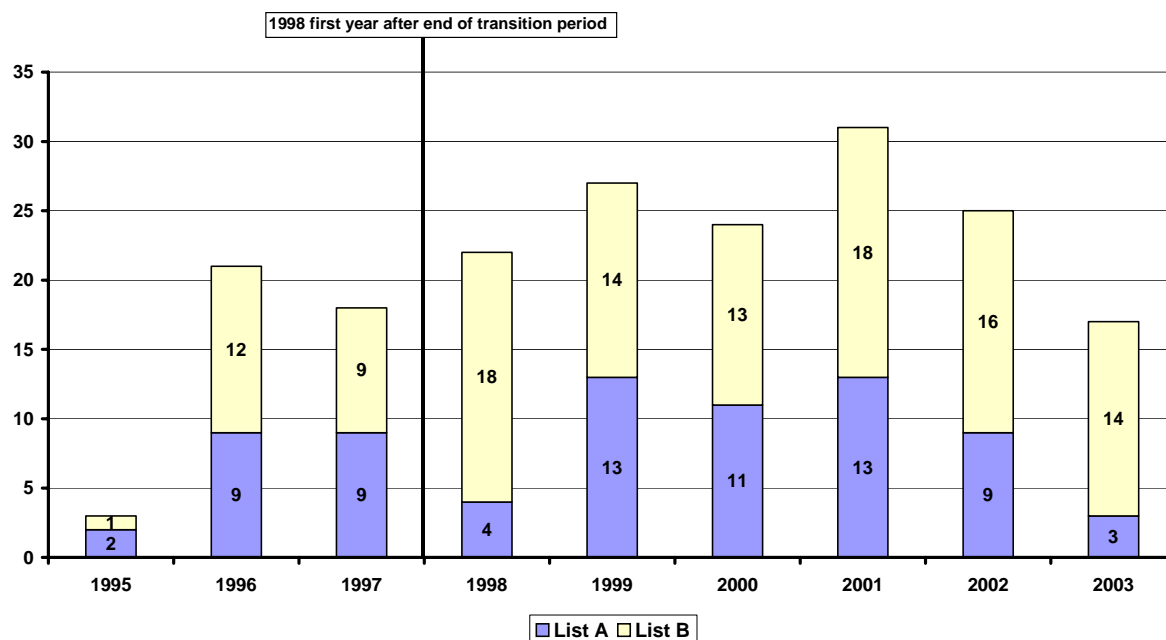


Source: EMEA

Figure 8 also shows a longer time series as we included the years 1995 to 1998. Note that these years reflect the introduction of the new application regime and is therefore not fully comparable with the other years. However, the number of applications in these years provide a lower bound of the applications we would have observed had the system been fully introduced at the time. Thus, it is interesting to note the very high number of applications in the year 1997.

The picture changes when considering the number of authorisations (see Figure 9). Here the years 1997 and 1998 show one of the lower numbers of applications. This is consistent with the high failure rate of 37% reported for the year 1998.

Figure 9: Number of List A and List B marketing authorisations for NAS granted by the European Commission under the centralised procedure per year

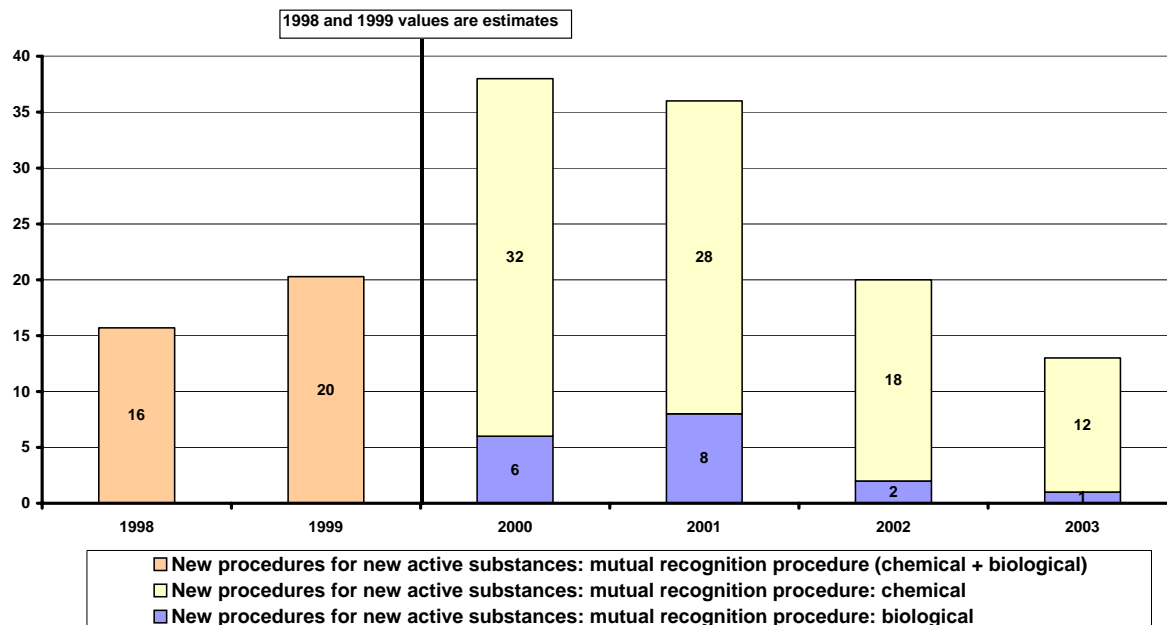


Source: EMEA

Figure 9 also shows that authorisations for List A and for List B products have fallen. However, in percentage terms the fall has been more pronounced for List A products. Comparing the years 2001 and 2003 we find that the percentage decrease is more significant for List A products (-77%) than for List B products (-22%).

Figure 10 and Figure 11 below refer to the mutual recognition procedure. Figure 10 clearly shows a downward trend in the number of applications under the mutual recognition procedure.

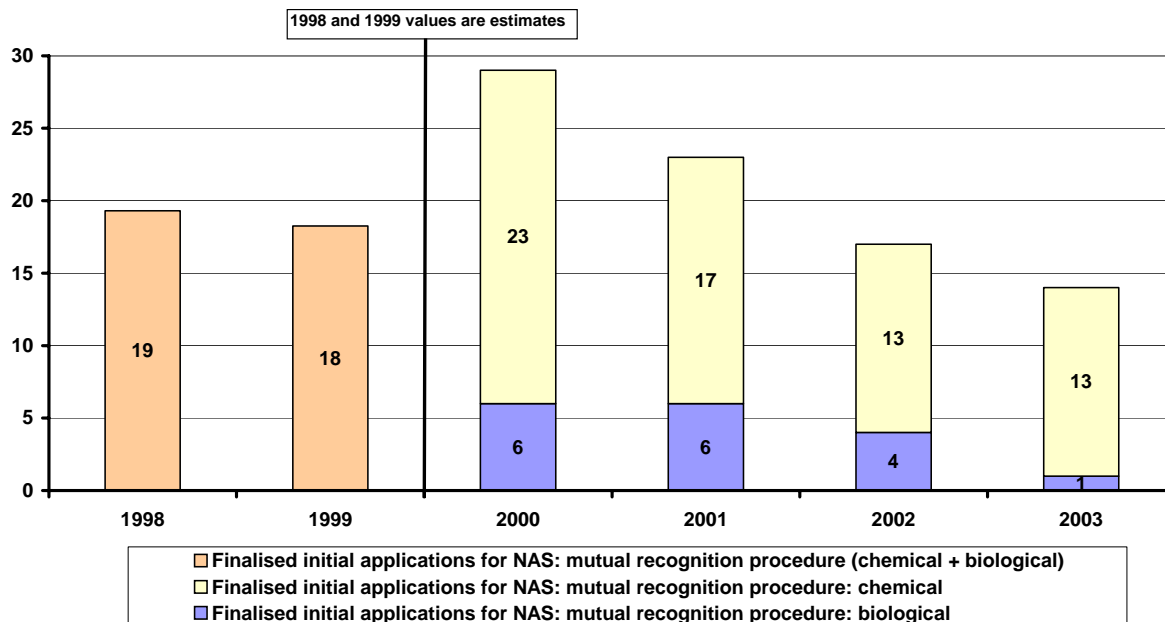
Figure 10: New mutual recognition procedures started for new biological and chemical substances



Source: EMEA. Due to data non-availability, 1998 and 1999 figures are estimates for chemical and biological substances combined, based on the assumption that 65% of total new NAS applications (24 in 1998 and 31 in 1999) were initial applications (average share of initial NAS applications in 2000, 2001 and 2003; 2002 excluded due to unavailability of November data).

Since 2001 this trend holds for new biological (-88%) and for chemical substances (-57%) and is also reflected in the lower number of finalised procedures that lead to authorisations in the Member States (see Figure 11).

Figure 11: Finalised initial applications under the mutual recognition procedure: new biological and chemical substances



Source: EMEA. Due to data non-availability, 1998 and 1999 figures are estimates for chemical and biological substances combined, assuming that finalised initial applications are 52% of total finalised applications for NAS (37 in 1998 and 35 in 1995; 52% is the average relationship of initial and total new NAS applications in 2000-2003).

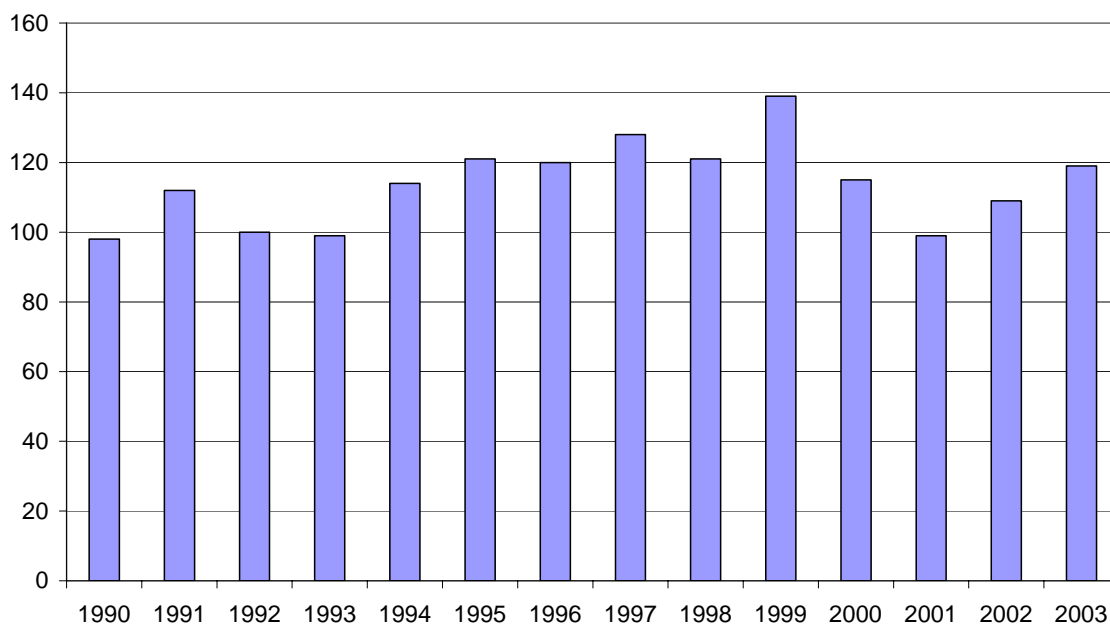
3.3.2 UNITED STATES

In the United States, the Food and Drug Administration (FDA) provides a considerable amount of data regarding applications and authorisations. Below we use this to:

- Examine the level of innovation in the US; and
- Compare the US experience with regard to the level and trend of applications and authorisations to the experience with the centralised and mutual recognition procedures in the European Union.

As shown in Figure 12 we see an increase in applications for new drugs (this includes only new chemical drugs for human use and therefore excludes biologics which are discussed separately below) during the mid 1990s and then a peak number of applications in the year of 1999 before a subsequent decline and recent recovery.

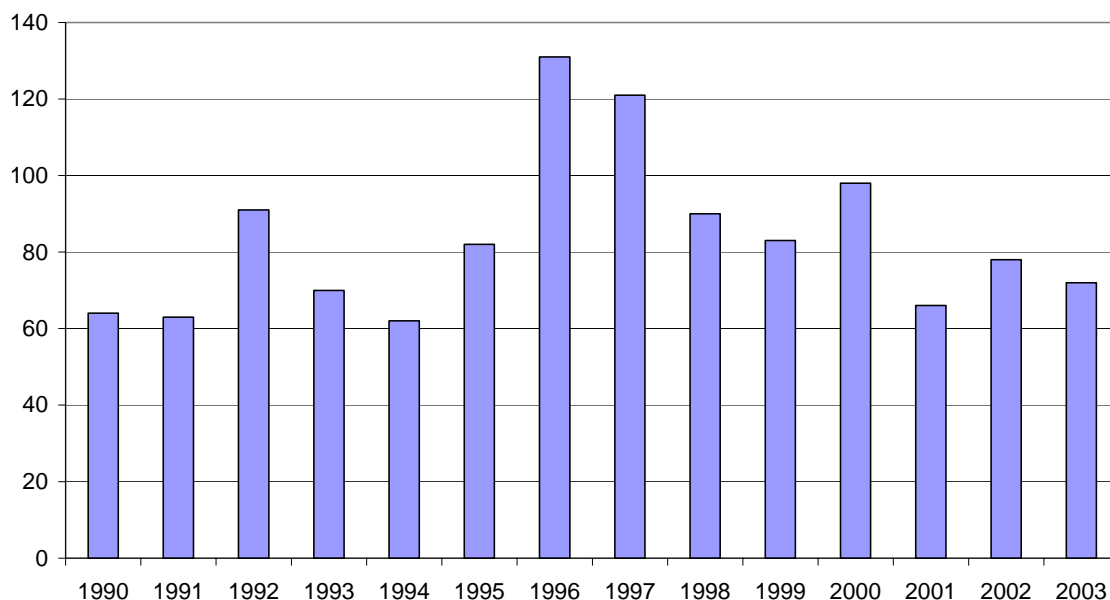
Figure 12: NDA applications received – 1990 to 2003



Source: FDA <http://www.fda.gov/cder/rdmt/>

Surprisingly the picture for approvals does not seem to closely follow the path of applications. Although there was a clear increase in the applications in the mid 1990s preceding the increase in approvals, there has been no reduction in the level of applications to explain the sharp fall in approvals in 1998. The peak in 1996/7 in approvals therefore stands out and cannot be put down to changes in applications. Leaving aside these two years there is a close correlation between applications to approvals two years afterwards.

Figure 13: NDA applications approved – 1990 to 2003



Source: FDA <http://www.fda.gov/cder/rdmt/>

In Table 4 below we consider the correlation between applications submitted and approvals since 1990. We find there is a positive correlation between contemporaneous applications and authorizations. Taking into account the average application process (16-19 months²²) we surprisingly find the correlation falls to 0.01. Leaving out the exceptional periods 1996 and 1997, however, the correlation raises to 0.7.²³

²² Source: Tufts CSDO 2003 and FDA website for all NDAs applications (excluding biologics).

²³ The exceptionally high level of approvals has been investigated by a number of authors. Tufts found the number of approvals in the three years 1996 to 1998 exceeded the second highest three-year total of approval since 1962 by 49 percent. They attributed the surge in approvals to an increase in the number of NDAs, an improvement in the quality of NDAs submitted, and an approval time that was 31 percent faster than in the previous three-year period. At the same time as the surge, questions concerning whether faster FDA review times and fewer drugs approved in the US with prior foreign marketing had compromised the safety of the country's drug supply. Evidence at the time suggested that this was not the case and that relabeling for serious adverse events had actually dropped during this time, but the FDA did begin to focus on drug safety. Kaitin, Kenneth I. And Elaine M. Healy. "The New Drug Approvals of 1996, 1997, and 1998: Drug Development Trends in the User Fee Era." Tufts Center for the Study of Drug Development, 2000.

Table 4: Correlation between applications and authorisations²⁴

Correlation between:	Correlation coefficient
Applications and authorisations	0.45
Application lagged by two years and authorisations	0.01
Application lagged by two years and authorisations (excluding 1996/7)	0.7

Source: FDA and CRA calculations

Assuming this relationship is stable we would therefore expect the number of approvals to increase over the next two years.²⁵

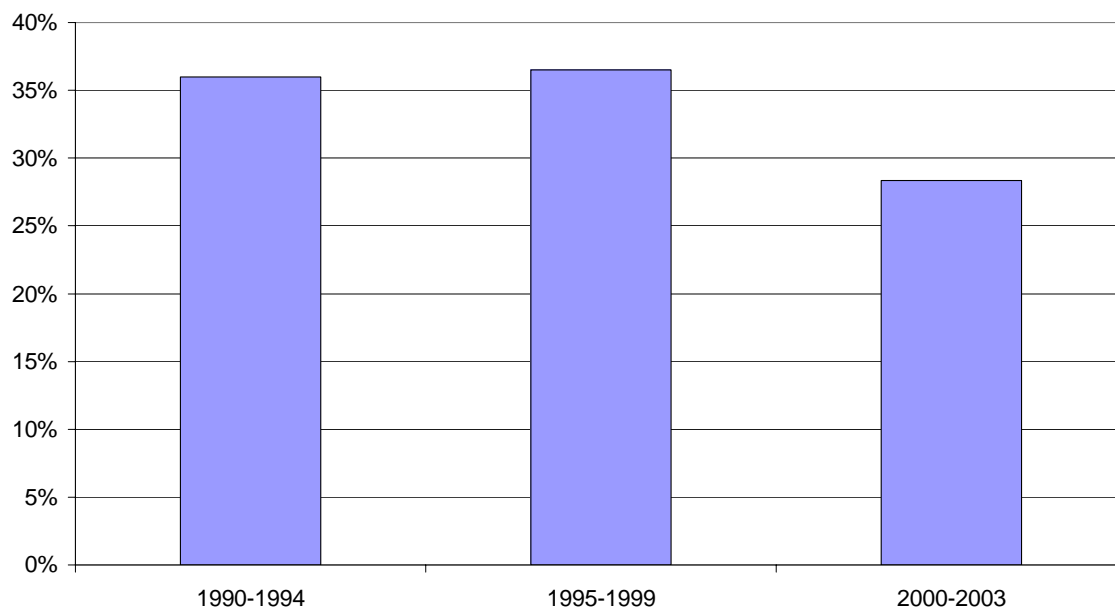
As we can see the recent performance of the US has not been dissimilar to the development in Europe with a significant fall in the number of applications and approvals. As in Europe there appears to be a recent small recovery in the US in terms of applications and authorisations. However, to be comparable to data from the EMEA and MRFG we need to consider new active substances, which involves removing new approvals for indications, formulations etc and including biologics.

Differentiating new molecular entities from other approvals it is clear that the proportion of NMEs has fallen over the last five years (as set out in the Figure 14 below)

²⁴ Correlation is a measure of association between two variables. The higher the correlation the more highly related the two variables. This table compared the correlation between contemporaneous applications and authorisation to that of lagged applications and authorisations.

²⁵ It is not possible to get data on the number of withdrawals or negative decisions by the FDA, so we have not been able to replicate this analysis for the US market.

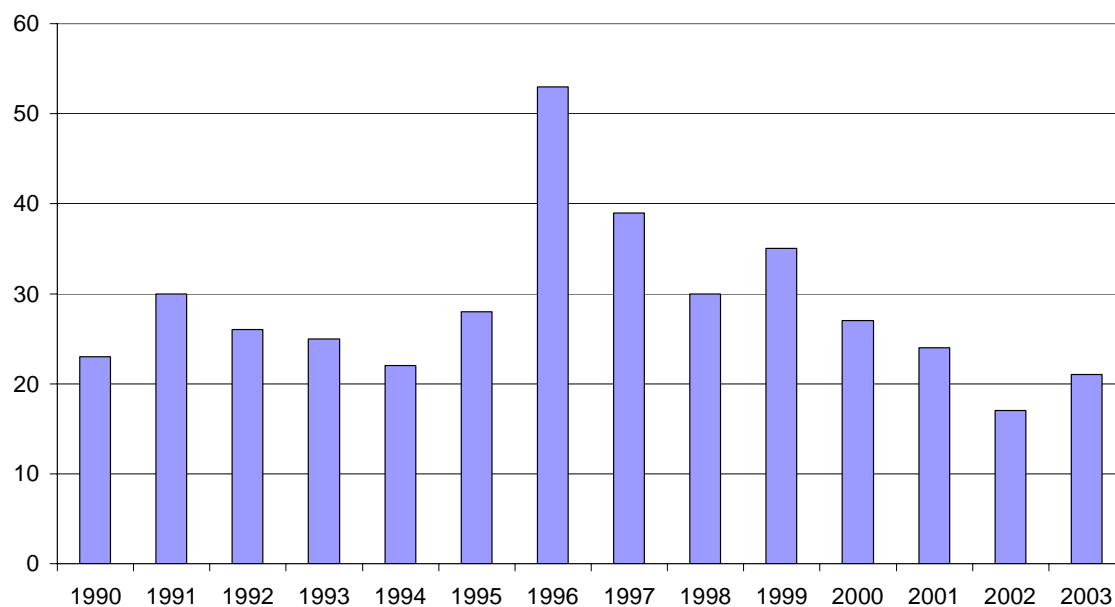
Figure 14: NMEs as % of NDAs



Source: FDA <http://www.fda.gov/cder/rdmt/>

This has resulted in a substantial bigger drop in NMEs approved than in new drug applications - as the number of approvals has fallen so has the percentage of approvals that are NMEs.

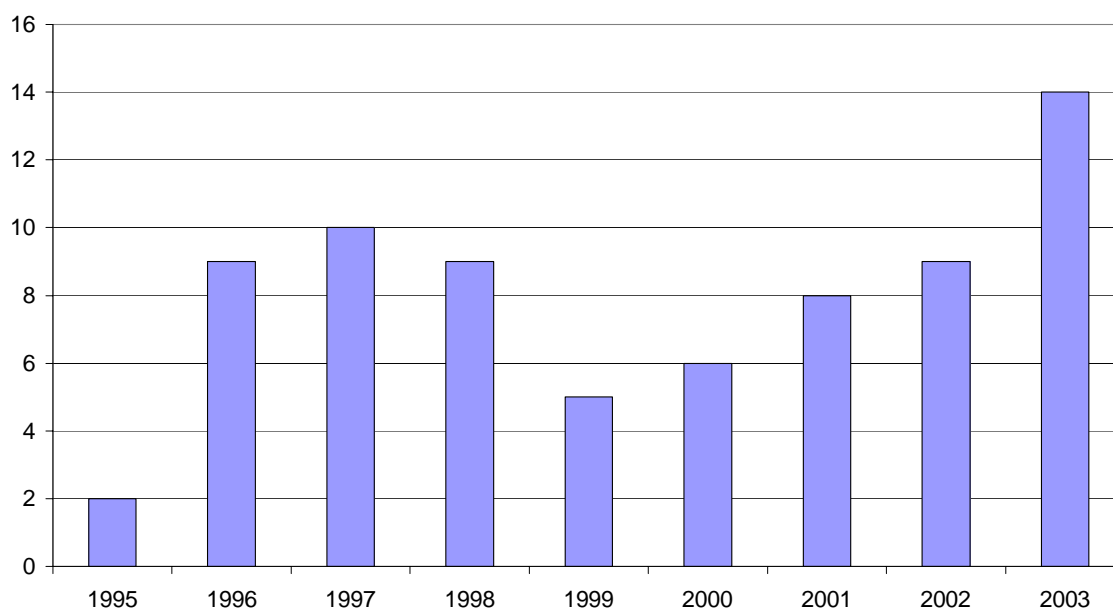
Figure 15: NMEs approved



Source: FDA <http://www.fda.gov/cder/rdmt/>

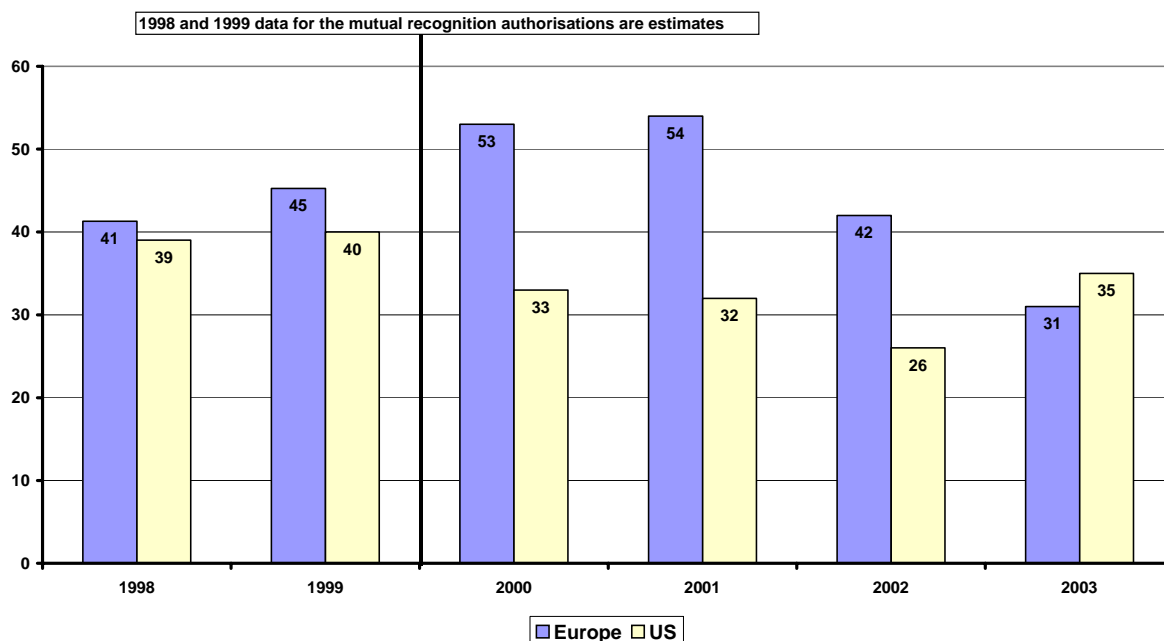
However, to compare this to the European data above we need to include new biologic product. These are authorised by a separate division of the FDA. The FDA data on biologics are considerably less developed than new chemical drugs. Unfortunately, it is only possible to get data on authorisations rather than applications for new biologic products.²⁶

Figure 16: New biologics approved



Source: <http://www.phrma.org/newmedicines/resources/2003-01-30.102.pdf>

²⁶ The increase in biologics was foreseen, in the early 1990s, DiMasi saw the growth possibilities of the biopharmaceutical market: “If the NDA submission success rates for biopharmaceuticals are similar to those for chemical drugs, we may expect an increasing number of new drug approvals in the mid to late 1990s. The proportion of the mid- to late-1990s approvals that are for biopharmaceuticals should also increase over time.” DiMasi, Seibring and Lasagna (1994), p. 620.

Figure 17: Comparison of authorisations in Europe and the US

Source: EMEA and FDA. EMEA data include both the centralised and mutual recognition procedures. FDA data include all NMEs and BLAs.

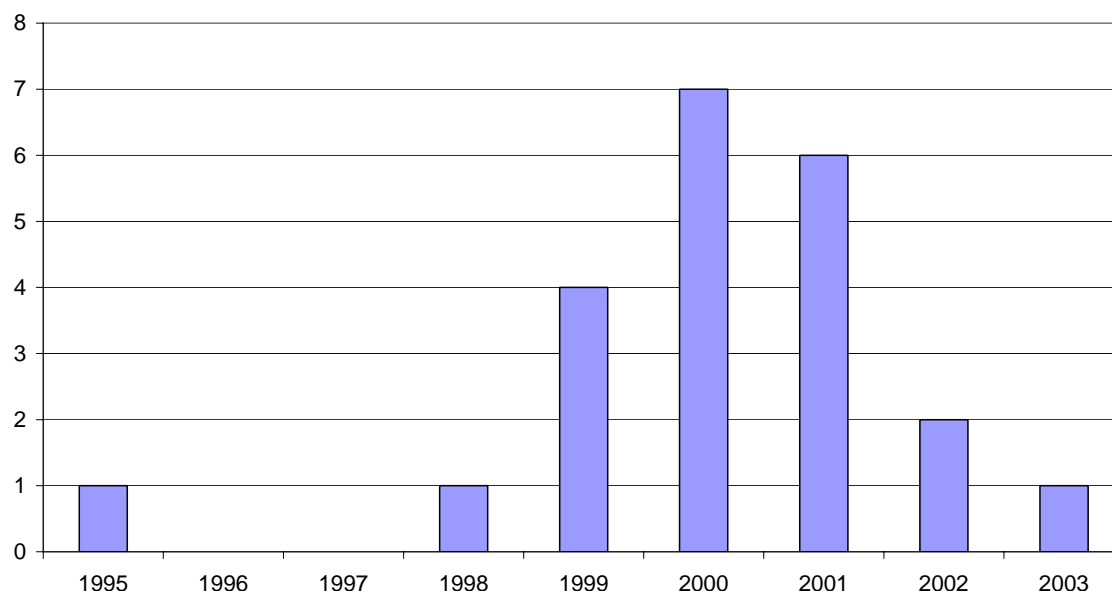
Figure 17 shows the comparison of authorisations for new active substances in the US and Europe. This comparison shows a divergent path over the last five years. In particular, European authorisations continued to grow in 2000 and 2001 whilst the US authorisation fell but recovered in 2003. To investigate this further we examined authorisations under the centralised procedure and by the FDA in 2001.

3.3.3 COMPARISON OF US AND EUROPEAN AUTHORISATIONS IN 2001

To investigate the relationship between European and US authorisations we have looked at new chemical entities authorised by the FDA and new active substances authorised under the centralised procedure in the European Union in 2001.

Under the centralised procedure, there were 31 new active substances authorised in 2001, of these 22 had been approved by the FDA either as a biologic or as a new chemical entity at this point in time, a further 5 had been submitted but not yet approved. We could not find any evidence that 4 of these products (representing 13% of products approved under the centralised procedure) were going through the application process in the US. In Figure 18 below we examine the timing of these authorisations.

Figure 18: Timing of authorisations by the FDA of products authorised under the European centralised procedure in 2001

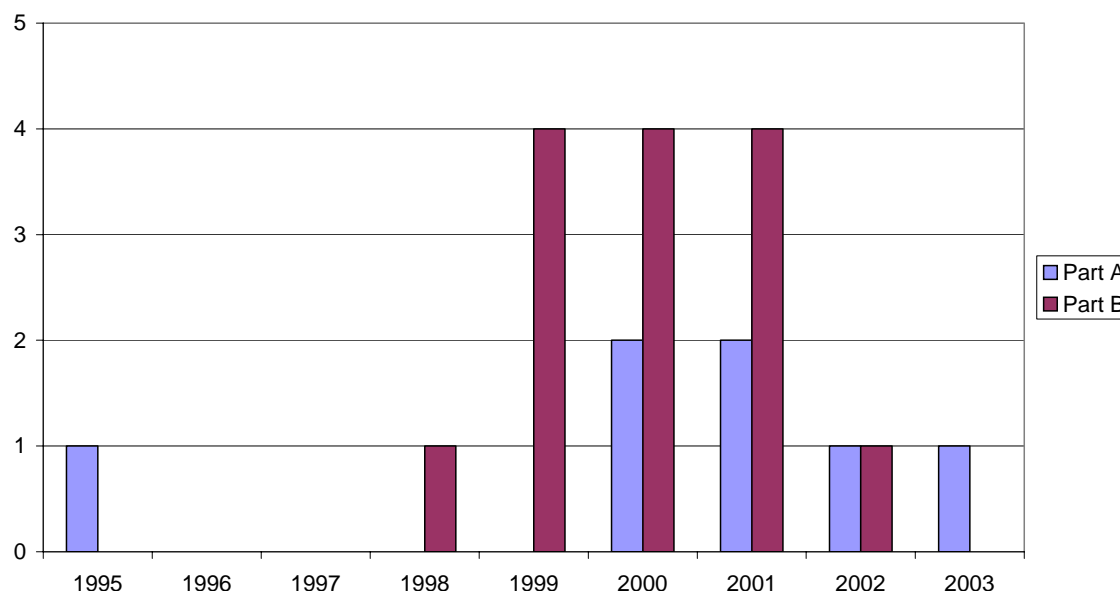


Source: FDA, EMEA and CRA calculations

That is, of the products authorised under the European centralised procedure in 2001, one product was authorised by the FDA in 1995 and another in 1998 and so on.

It is clear from this analysis that the majority of authorisations approved by the FDA happened before the centralised procedure approval: 86% were approved in the same year or earlier than in the European Union. However, taking into account the 5 currently going through the FDA process, this falls to 70%. This would provide some evidence that approvals were generally occurring earlier in the US but the difference is not large.

Figure 19: Timings by the FDA distinguishing between Part A and Part B products authorised under the European centralised procedure in 2001



Source: FDA, EMEA and CRA calculations

Breaking these down into part A and part B authorisations, we find that part A drugs are as likely to be authorised earlier as later in the US compared to Europe, whilst part B drugs are more likely to occur earlier in the US. That is, of the Part B drugs authorised under the centralised procedure, one was authorised by the FDA in 1998, but four were authorised in 1999, 2000 and 2001 respectively.

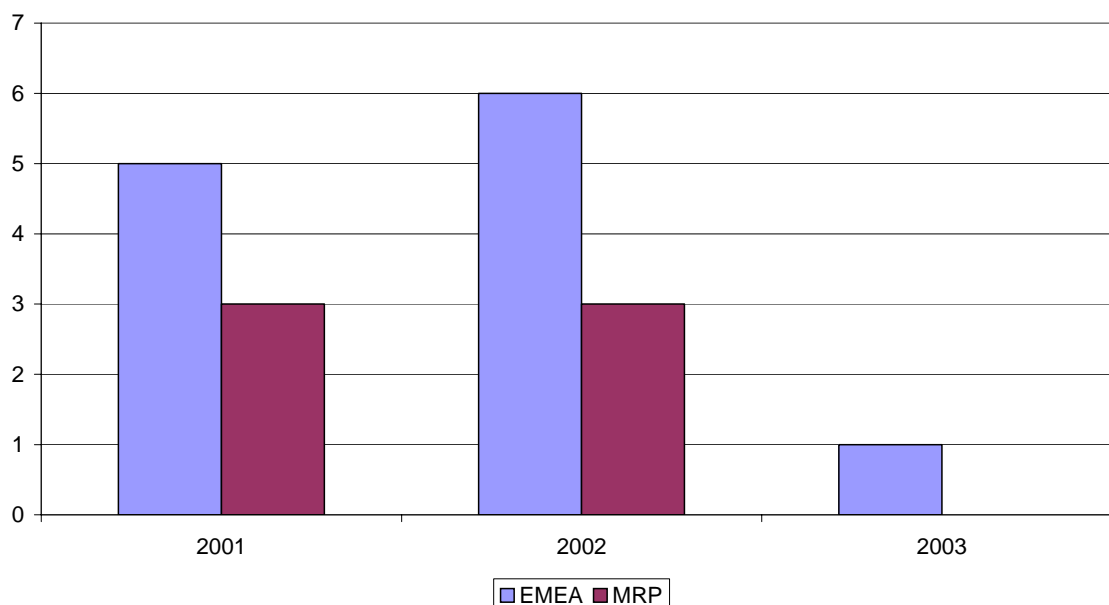
Looking at the FDA approvals (but only considering NCEs) in 2001, we find 24 product approvals. Of these, 12 have been approved under the centralised procedure and 9 have been approved by the mutual recognition procedure.²⁷ Similar to the US, we find about 13% of the products in the EMEA data where there is no evidence of applications or approvals taking place. Looking at the timing of applications, we find that all of the authorisations in Europe were in the same year or after the FDA approvals.

In conclusion, this shows how interlinked the European and US pharmaceuticals markets are. If products are authorised under the European centralised procedure or by the FDA, it is highly likely it will be launched in the other jurisdiction, the question is more when than if.

²⁷

In fact, one of these products has been authorized by the centralised and the mutual recognized process. The information on the products that have been approved under the mutual recognition process stems from the European Mutual Recognition Product Index (<http://mri.medagencies.org/prodidx/>).

Figure 20: Timing of authorisations under the centralised and the mutual recognition procedure



Source: CRA calculations based on EMEA and MRP data.

However, these results show the necessity of comparing FDA data to authorisations through both the centralised and mutual recognition procedure. The results also support that the European data appear to lag the US data. This is consistent with the expectation of a recovery in authorisations in Europe this year, following the recovery observed in the US in 2003.

The analysis of authorisations under the centralised procedure and by the FDA suggest that the higher number of authorisations in Europe appears to be due to variation in the mutual recognition process. However, at this stage it is difficult to determine whether this reflects:

- Products going through **both the** mutual recognition and centralised process (although this seems unlikely);
- A transitory catch-up of products launching in Europe; and
- Local products being authorised in Europe via the mutual recognition process that are not launched in the US.

Equally, the trend in biologics is a source of potential concern. In the US, new authorisations have grown due to the increasing number of biologics on the market. In Europe, recent years have seen a significant decline in biologics authorised by the mutual recognition procedure. Unfortunately, there is no data available on the number of biologics approved through the centralised procedure. However, at the CRA roundtable, industry experts shared the concern that the EU is lagging behind the US in terms of the development of biologics. Appraising this lag in quantitative terms is complicated by changes in the definition of the data, but there

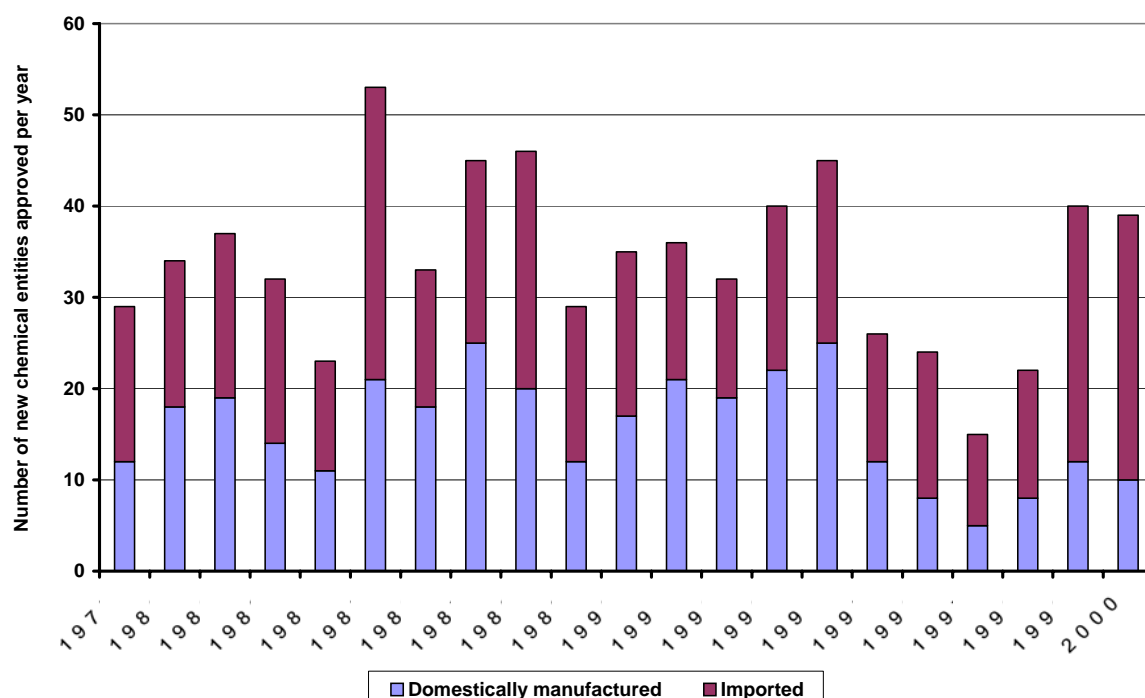
appeared to be agreement among the roundtable participants that the US was stronger in biologics than Europe. According to the discussion at the roundtable, possible underlying reasons include the higher number of biotech companies in the US, the fragmented European regulatory system for approving biologics and the lack of venture capital for small biotech firms in the EU. A controversial issue was also whether possibly weaker relationships between smaller biologics companies and big pharma in the EU played a role or not.²⁸

3.3.4 JAPAN

In Japan, the number of approved NCEs has been very volatile since 1980. The general trend appears to be downward, but in 1999 the number of newly approved NCEs almost doubled compared to the year before. The main reason for this upsurge seems to have been a strong growth in the number of imported NCEs. The number of domestically manufactured products increased too, but at a much lower rate.

Unfortunately, we have not been able to identify any data on the number of marketing applications in Japan.

Figure 21: Number of new chemical entities approved in Japan



Source: Parexels R&D Statistics 2003/2004, p. 296 and Koho (1987).

²⁸ For a detailed description of the discussion, see the notes on the CRA roundtable in Appendix IV.

Despite the downward trend in the number of new marketing authorisations over time, the Japanese government does not seem to be overly concerned about a decrease in the number of new products in the future. Contrarily, according to a report by the Ministry of Health, Labour and Welfare, there seems to be confidence that within the next decade, there will be very many new products coming out of the companies' pipelines, due to genomic drug discoveries ("a "gold rush" age for new drugs"). Yet, there are concerns that, due to the relatively low level of R&D expenditure in Japan compared to the US and a fall in the number of clinical trials in Japan, that Japanese companies might not be able to compete successfully in this new era.²⁹

3.4 Analysis by types of drug

Clearly, the number of new active substances is only part of the story and there are many other important measures of innovation. In this section, we look at the evidence that exists regarding:

- The therapeutic value of new products. It is often claimed that the pharmaceutical industry is only producing so called "me-too" products that do not offer anything distinctive to consumers, alternatively, it is often said that there is an over-emphasis on blockbuster products at the expense of incremental innovation;
- The patient population that will benefit from innovation in new drugs. In particular, there is increasing focus on encouraging innovation for smaller patient population that would otherwise not receive sufficient attention, these are designated as Orphan products;
- The number of line extensions to existing products. A new innovation for an existing product could offer as large a benefit to society as an entirely new compound;
- The distribution of market value. Clearly an indirect measure of the value of innovation is what society is willing to pay for it.

3.4.1 BY THERAPEUTIC VALUE

In terms of therapeutic value, we have not found a European source of data that allows us to make a meaningful comparison of this kind as stated in Section 2.2. We investigated two alternatives:

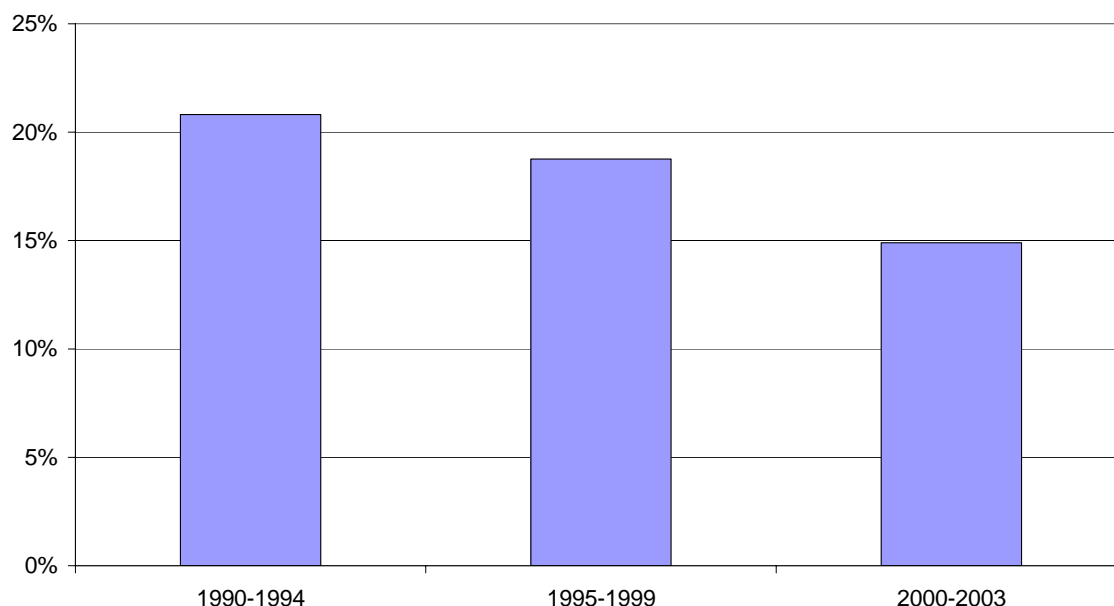
²⁹ Ministry of Health, Labour and Welfare of Japan (2002).

1. At a European level, the EMEA, since 1996, provides the option of an accelerated evaluation procedure for products for serious diseases.³⁰ For these products, the CPMP may adopt an opinion within the first evaluation period, i.e., 120 days, subject to the quality of the application, rather than the standard 210 days. An accelerated evaluation “might be initiated by the CPMP in exceptional cases when a medicinal product is intended to provide answers to major public health need, defined by three cumulative criteria: (1) the seriousness of the disease (e.g. heavy disabling or life-threatening diseases such as AIDS) to be treated; (2) the absence or insufficiency of an appropriate alternative therapeutic approach; (3) the anticipation of high therapeutic benefit.” Unfortunately, we have learned from the EMEA that the accelerated evaluation procedure has not been used in the past.³¹
2. A number of countries apply their own method of measuring therapeutic value, but these data are constrained by the products approved in that country, the publication of statistics and the period covered.

Although, not ideal, we have looked instead at the picture in the US. The FDA uses a classification that allows us to identify investigational new drug applications and new drug applications by their drug's chemical type and potential benefit. Taken at face value, the FDA data therefore allow us to differentiate between new substances replicating the benefits of an existing product (i.e. a me-too) and a truly innovative therapy. If we first consider whether new drug approvals are via the priority or the standard process, we find that the number going through the priority channel has fallen quite dramatically over the last ten years, from over 20% to only 15%.

³⁰ The respective document was updated in 2001 in order to clarify when an accelerated review can be granted.

³¹ Between 1995 and 1999, the EU approved 6 of the 27 new biopharmaceutical products “under exceptional circumstances,” this contrasts with the FDA approving 11 with a priority review. However, it is unclear that approval under exceptional circumstances is comparable to priority review. “Impact Report: European approval of new biotech drugs outpaces US approval.” Tufts Center for the Study of Drug Development, March 2000.

Figure 22: The percentage of NDAs approved by the FDA through the priority process

Source: FDA <http://www.fda.gov/cder/rdmt/>

However, it should be also noted that there were significant changes in the US system over this period making this comparison problematic.

Analysis based on data from the FDA therefore suggests a shift in the mix of products approved. However, although this is the ‘best’ measure of therapeutic value available it is by no means ideal. In particular, it excludes the increasing number of drugs that are biological. Therefore, although there is a cause for concern, the jury is still out on whether the social value of new products is falling.³²

3.4.2 ORPHAN DRUGS

We can also look at the pattern for Orphan drugs.³³ Orphan drugs first appeared in the centralised procedure in 2000, when applications for two List A products with orphan designation were registered at the EMEA. Applications for List B products started in 2001 – at a higher level than applications for List A products as one would expect given the wider

³² There are a number of papers representing different views in the US debate regarding innovation. For example, the National Institute for Health Care Management set out the case for a reduction in innovation in their report “Changing Patterns of Pharmaceutical Innovation.” NIHCM, May 2002. However, the US trade association (PhRMA) responded setting out the difficulties in using products authorised through the priority channel as a measure of innovation. In particular, they highlighted the increase in the number of biologics and vaccines and an increase in drugs in preclinical trials.

³³ Where an orphan drug has received a designation as a treatment of a rare disease requiring additional regulatory support.

coverage of List B. Applications for both List A and B orphan products remained relatively stable until 2002, but decreased in 2003 compared to the previous two years. However, total orphan drug marketing authorisations have slowly, but continuously increased since 2001.

Unfortunately, we only have a very short time series available for the analysis of orphan drugs in Europe. Hence, we cannot draw strong conclusions. Still, it seems that the share of orphan drugs in total applications and authorisations in Europe has increased significantly since 2000. Especially the share of applications for orphan products increased dramatically between 2000 and 2002 (from 5% to 44% of total centralised applications), but fell to 21% in 2003. In contrast, the share of orphan drugs in total centralised marketing authorisations has increased more moderately but steadily, from 10% in 2001 to 29% in 2003. Unfortunately, we cannot disentangle the increase that is due to the introduction of the orphan products policy in 2000 and an increase that reflects a long-term trend.

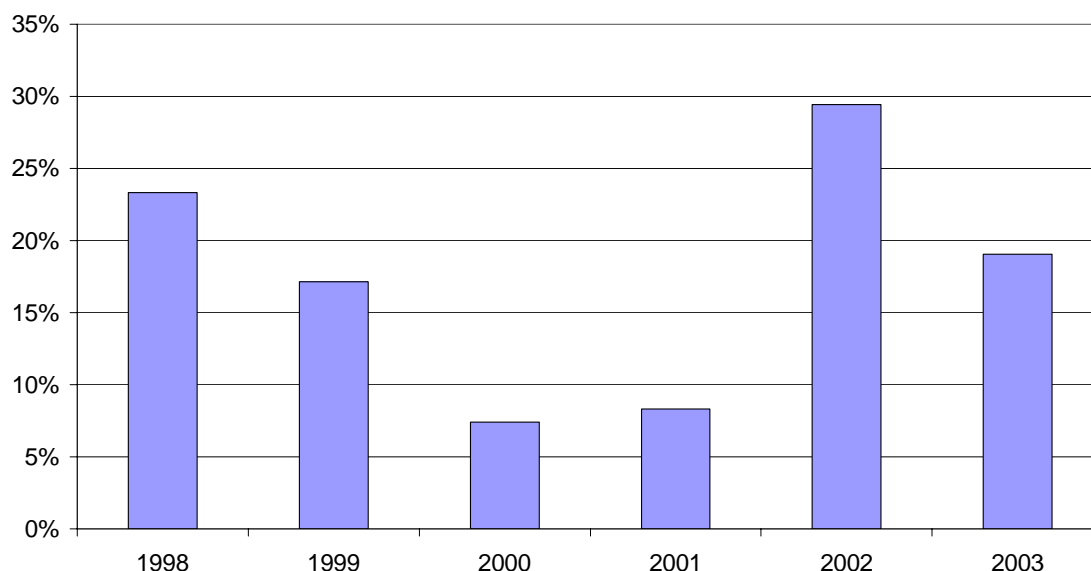
Table 5: Orphan drugs under the centralised procedure – applications to the EMEA and marketing authorisations granted under the centralised procedure

	2000	2001	2002	2003
Orphan drug applications total	2	12	11	7
- of which List A	2	2	2	0
- of which List B	0	10	9	7
Orphan drug applications as percentage of total applications	5%	32%	44%	21%
Orphan drug marketing authorisations total	0	3	4	5
- of which List A	0	2	1	1
- of which List B	0	1	3	4
Share of orphan drug authorisations in total authorisations	0%	10%	16%	29%

Source: EMEA

In the US, orphan drug designation has existed for much longer, with the first market approvals for orphan drugs in the early 1980s. Market approvals grew substantially during the 1980s increasing from 2 to 12 per year. Over the last fifteen years, although there has been substantial variation, these have averaged about 13 a year. As shown in Figure 23, this is also the case for the proportion of NMEs that have Orphan drug designation.

Figure 23: Designated Orphans drugs as % of approved NMEs in the United States

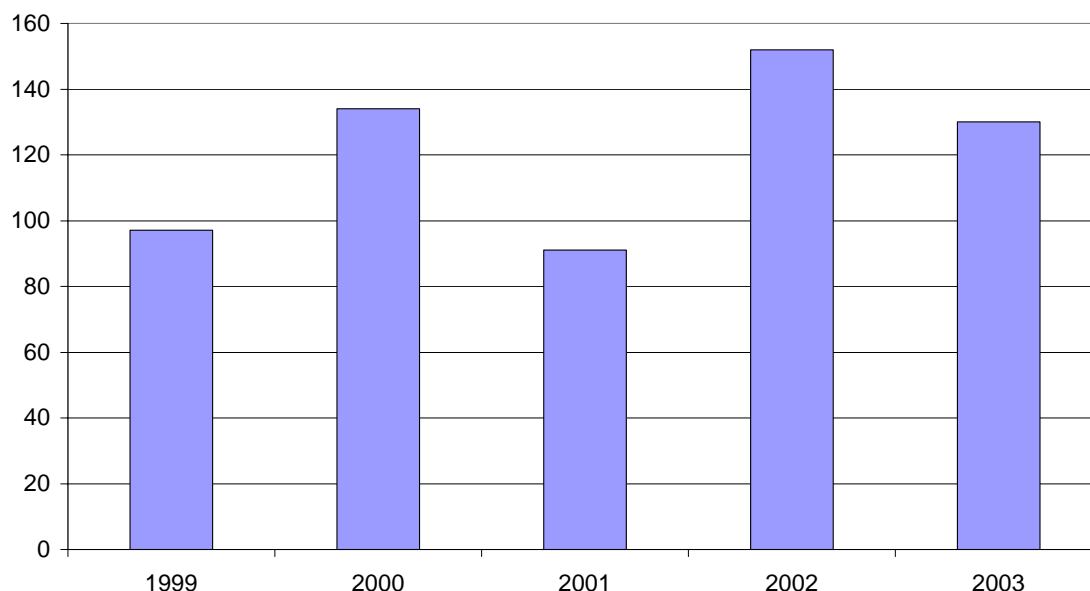


Source: <http://www.phrma.org/newmedicines/resources/2003-01-30.102.pdf>

The future of Orphan drugs is substantially a policy decision. Based on the recent reduction in applications and the evidence from the US, it would not be unreasonable to assume that Europe is approaching a steady state level of orphan products.

3.4.3 NEW INDICATIONS

In the US, since the beginning of 1994, new indications have been tracked as efficacy supplements, not as new drug applications. There is no evidence over the last five years, that the number of line extensions has increased dramatically (as shown in Figure 24 below).

Figure 24: Efficacy supplements in the United States

Source: FDA <http://www.fda.gov/cder/rdmt/>

Looking at the types of efficacy supplement, set out in Table 7, we find there is no observable trend in new indication (that would previously have been an NDA) or new or modified indications.

Table 6: Efficacy supplements over time

	NDA Type 6 - New indication	New indication	New dosage regime	New route of administrati on	Comparativ e efficacy	Patient Pop	Rx to OTC	Traditional approval updating fast track	Incorporate clinical trial results
1999	5%	44%	14%	0%	3%	3%	1%	2%	5%
2000	4%	46%	13%	1%	0%	6%	0%	3%	4%
2001	5%	32%	13%	1%	0%	15%	0%	4%	5%
2002	14%	41%	9%	0%	1%	22%	6%	7%	14%
2003	5%	39%	13%	0%	0%	13%	2%	2%	5%

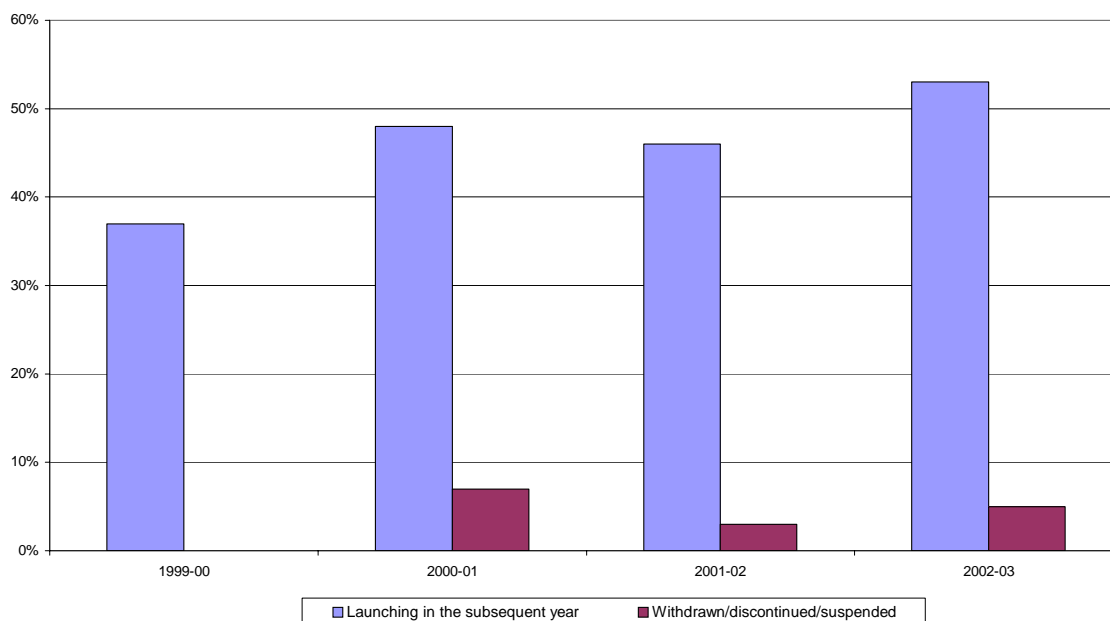
Source: FDA <http://www.fda.gov/cder/rdmt/>

3.4.4 THE VALUE OF NEW DRUGS

However, arguably the most important measure of innovation is new products and treatment actually becoming available to European consumers. It is possible that products get through the approval process and then do not launch, losing all the potential benefits. Equally, there is information in the amount spent of different treatments regarding how much it is valued.

To assess the first issue, we used IMS R&D Focus to look at the probability of a product that has successfully received market authorisation launching on the market in the next year over the last five years.

Figure 25: Probability of a registered product being marketed versus withdrawn in the subsequent year



Source: IMS R&D Focus

Looking at the short period for which we have IMS R&D Focus data, we can trace products that have successfully been authorised and determine whether they are marketed or withdrawn in the following year. Clear for a large proportion of products there is a delay before marketing which can take longer than a year, in which case they do not change status.

This analysis suggests there has been a small increase in the probability of a registered product launching in the subsequent year, with no corresponding decrease in the probability of being withdrawn. This would suggest that the time between launch is falling but the probability of a registered product getting to market is not changing.

Table 7: Analyst predictions of market value of pipelines (peak sales in US dollars)

Pipeline assessment	>800 Million	799-450 Million	449-350 Million	349-200 Million	199-0 Million
1995	3%	6%	24%	31%	36%
1999	15%	25%	5%	23%	31%
2001	20%	28%	4%	22%	26%
2003	17%	30%	8%	18%	27%

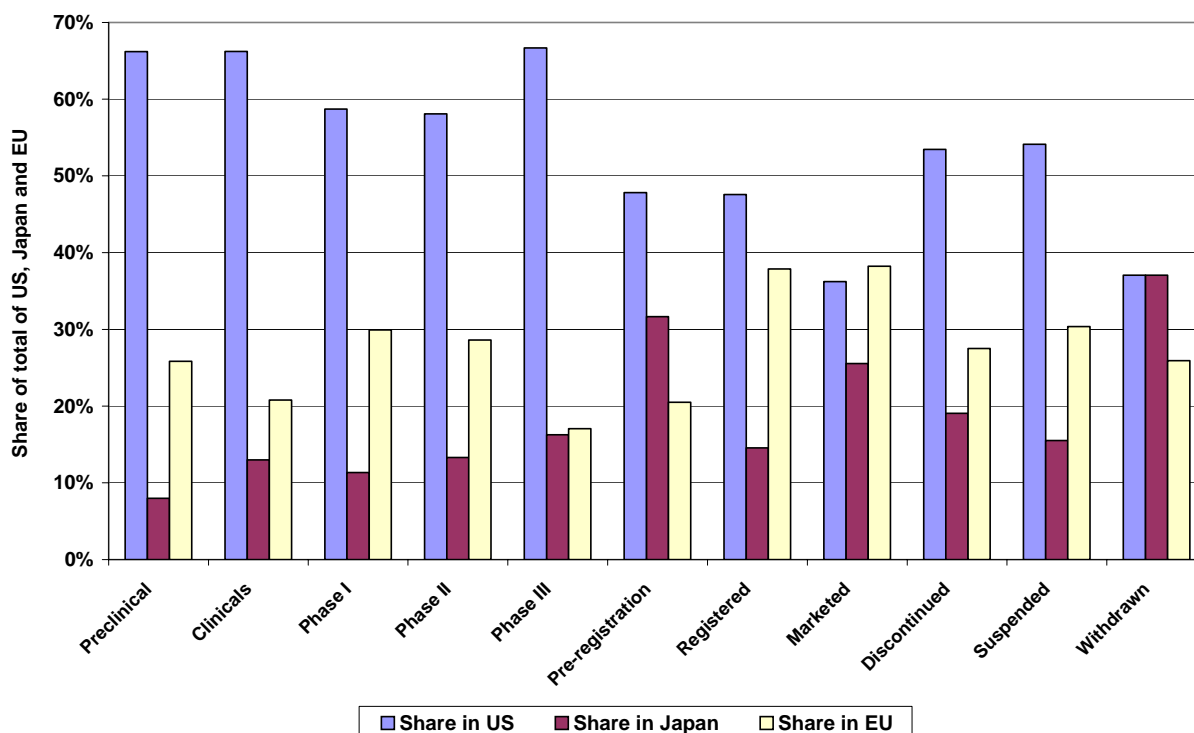
Source: Lehman Brothers

One way to measure market potential is via broker reports. To value pharmaceutical companies brokers invest considerable effort monitoring pipeline information and market potential. The best known of these is Lehman Brothers pipeline forecast. As shown in Table 7 above, there has been a significant change in the composition of the pipeline from the mid 1990s, when only 3% of products had a market potential over \$800 million. By 1999 this had risen by 15%. However, over the last five years, there has been relatively little change in the composition of the pipeline.

3.5 Geographical analysis

Finally, we considered geographical variation. The graph below look at the share of products in Europe, US and Japan by the stage of development: the US accounts for a significantly higher share of products in the early stages of R&D development than Japan and the EU. About two thirds of all products in preclinical and phase III development are based in the US. The share of the EU ranges from 17% for products in phase III to 38% for products that are registered and marketed.

Figure 26: Share of products in a particular development stage in the US, Japan and the EU in 2003

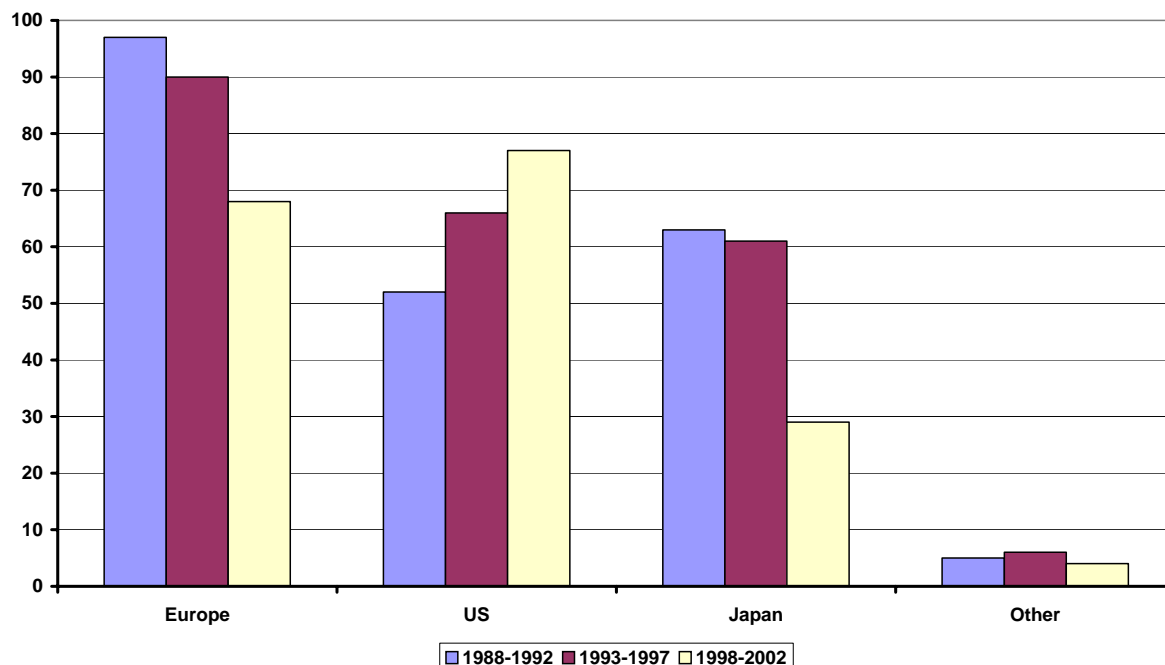


Source: CRA calculations based on IMS R&D Focus data.

The analysis above has focused on products in development, going through the regulatory process or launching in particular regions. We can also conduct the analysis by the nationality of the pharmaceutical company's involved. Figure 27 shows this analysis by the nationality of the mother company. This appears to show the importance of "European" companies has fallen quite dramatically comparing the last five years to the early and mid-1990s.

A similar picture emerges when we consider Japan. The US has been the clear beneficiary of this trend.

Figure 27: Number of new chemical or biological entities by nationality of mother company 1988-2002



Source: SCRIP-EFPI calculations (according to nationality of mother company), see *Efpi The Pharmaceutical Industry in Figures*, p. 16

3.6 Stylised facts

This analysis allows us to characterise the level of innovation currently observable in the European pharmaceutical industry:

- As is well known, the global level of R&D expenditure has risen dramatically over the last 20 years. There has been a substantial increase in R&D expenditure in Europe but this is at a lower rate of growth than the US. There is some evidence that this expenditure has focused on drug discovery and to lesser extent on clinical development;
- There has been an increasing number of products in preclinical testing in recent years, however, this has not translated itself into a proportionate increase in growth rate of the number of products going into clinical development;
- The picture in clinical development is mixed, we are seeing considerable growth in the early stages of development but we have not seen a corresponding increase in products in Phase III development and going through the approval process;
- There has undoubtedly been a fall in the number of product applications and authorisations in the United States over the last five years. This is especially worrying as the proportion of applications for new chemical entities has fallen more quickly;

- Comparing the pattern of applications and approvals in the EU and the US and following new approvals in 2001 under the European centralised procedure and by the FDA, this would appear to suggest this is a global phenomenon, rather than isolated to Europe. However, this comparison is complicated by products going through the mutual recognition procedure;
- Assuming this to be the case, the problem is exaggerated by trends in the types of products being developed:
 - Less innovative products – as proxied by drugs going through the priority process in the US, although on other hand biologics are increasing rapidly in the US. However, there is cause for concern that there does not appear to be same growth in the number of biologics in Europe, at least not under the mutual recognition procedure;
 - A delay between products being introduced in the US and getting to the European market.
- However, based on analyst data we find no evidence that there is greater focus on blockbuster products over the last five years, although there has been a significant change over the last decade.
- Finally, in terms of ownership there has been a substantial reduction in products that can be said to be developed by “European” companies. However, this effect may represent changes in ownership rather than differences in R&D innovation.

4 Phase I: Future levels of applications and authorisations

In this chapter, we consider the future evolution of new product innovation, as measured by applications, authorisations and launches. There are clearly a multitude of different ways of predicting the future (we have already discussed the results from using application data to predict authorisations), we start with the most simple, that is an extrapolation of current trends. We then consider a number of methodologies for improving the sophistication of our forecasts. These include:

- Using pipeline data for products currently in preclinical testing and clinical development and those already in the registration process;
- Learning from the long-term behaviour of approvals and authorisations, particularly from the US where we have a consistent time series over a long period of time;
- Consideration of a number of key technologies that have been identified as potentially important as a source of new products in the future.

All of these methodologies have their disadvantages and we should not rely on any individual forecast to draw strong conclusions.

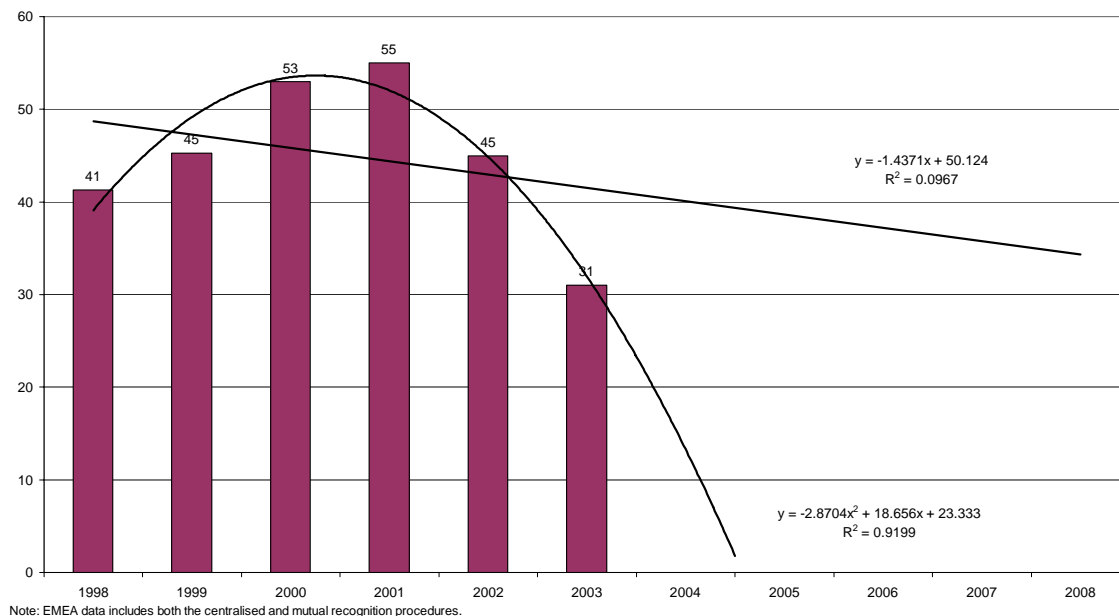
4.1 Extrapolation

4.1.1 EUROPEAN DATA (SHORT RUN)

Looking at new active substances approved in Europe by the centralised and the mutual recognition procedure, a very simple approach is to statistically fit a number of different models to create a simple extrapolation. In Figure 28 below we fit:

- *A simple linear model:* This predicts a gradual reduction in the number of products over time. However, as 2003 is an outlier (according to this model), the number of approvals is predicted to rise from 31 in 2003 to 35 in 2008. This model only explains 10% of the variation in our data and the time variable is not significant.
- *A quadratic model:* This predicts that the number of approvals continues to fall dramatically after 2003. In fact, continuing the trend as observed between 2001 and 2003 would predict the number of approvals falls to zero. Clearly, this model fits the data much better (explaining 91% of the variation) but does not yield common-sense results.

Figure 28: NAS authorised in the EU under the centralised and the mutual recognition procedure



Source: EMEA and MRFG and CRA analysis

From a statistical perspective, the quadratic model is the most appropriate model to extrapolate new active substances. However, given it predicts authorisation falling quickly to zero, we can rule this out by applying common sense.

Comparing the linear model, we would prefer a constant (predicting 45 new active substances in each year) to this simple linear extrapolation. These models support the conclusions we should not put too much weight on a small number of observations.

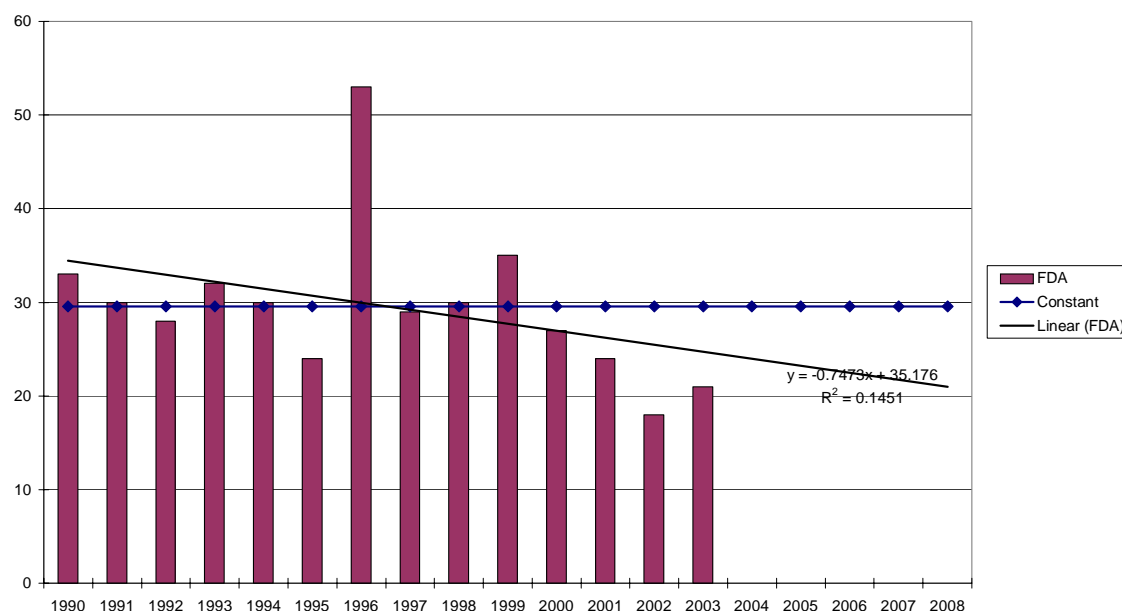
4.1.2 FDA DATA (SHORT RUN AND LONG RUN)

Simple analysis of the FDA approval for new molecular entities illustrates a number of points. If we look at the level of approvals from 1990, it is clear that the last four were below the long-run average. However, there is also considerable variation, with 1996 being almost double the average of the preceding six years. Again if we fit simple statistical models to these data it suggests:

- A trended model would suggest a declining number of approvals over time – however, the time trend is not statistically significant;
- Modelling the number of approvals as a constant (29 per year). Given the variation around this estimate, only 1996 would stand out as exceptional;

- The variation in recent years, i.e. 2001 and 2002, is not individually statistically significant.

Figure 29: NMEs approved by the FDA



Source: FDA and CRA analysis

This would suggest there is a real danger looking at the last five years and drawing strong conclusions given the level of variation we would normally expect. From a statistical perspective the best model would be to assume the next period is the long-term average.

4.2 Pipeline data

However, a simple extrapolation of current trends in applications and authorisations does not exploit information we already have regarding future products. Before a product applies for authorisation or is approved, the product will be in clinical development and prior to this in preclinical testing. For the purposes of this project we have collected data from 1999 to 2003 of all products in preclinical testing and clinical development from IMS's R&D Focus.

4.2.1 USING IMS DATA TO CREATE A SIMPLE FORECAST

From the snapshot of products in development in 2003 we have a foundation for creating a forecast. This requires:

- An estimate of the length of time taken to go through each phase. This allows us to predict how long it will take for a product to get from Phase I to Phase II, from Phase II to Phase III and so on.
- A probability that the product will get to the next development phase, since clearly not all products are launched, get approval or even move from one phase to the next. Any forecast needs to account for the number of products that fail.
- A probability that the product will be successful in getting through the application process.

As a proxy for all of these requirements, we have looked at the movement of products through the various development stages per year.³⁴ In particular, we estimate the transition probability of products between phases, i.e. determine how likely it is that a product that was in a certain phase in year 1 will be in another phase in the following year. For example, in Table 8, the probability that a product that was in preclinical in 1999 will be in preclinical in 2000 is 89% . A product that was in pre-registration in 1999 had a probability of 26% of being marketed in the following year.

Our approach covers all requirements set out above. First, it provides an implicit estimate of the length of time needed to go through each phase: if the time needed to go through a phase is at least one year, we will see products moving gradually from one phase to the next. If the time needed to go through a phase is lower than one year, we will see products jumping from e.g. phase I to phase III from one year to the next without showing up in phase II at all. Second, the annual transition probabilities will by definition cover the requirements for the probability of a product to move to the next phase of development and to get through the application process.

The approach described above seems straightforward, but has the implicit assumption that probabilities of success will be constant over time, which there is good reason to believe is not the case.³⁵ Indeed, there are arguments that until the impact of new technology has worked through the length of time for a product to move to the next phase could increase. This forecast would therefore represent an upper bound and needs to be considered in this light.

Estimating transition probabilities is the first step in forecasting the expected level of new product authorisation in Europe for 2004-2008.

³⁴ We restricted our analysis to products that IMS reports as being in development, marketed, withdrawn or discontinued in at least one EU member state, the EU or Europe as a whole, Benelux, or Scandinavia. We group products by their “latest phase” as reported by IMS, which means that not all products classed as e.g. “phase III” are actually in phase III in Europe (they might be in phase I in Europe and in phase III in the US). In our forecast, we apply a “European adjustment” based on the share of products reported as being in latest phases marketed or registered that were actually marketed or registered in Europe during 1999-2003.

³⁵ See discussion at the CRA Roundtable in Appendix IV.

Estimating transition probabilities

In our analysis of the annual transition probabilities for a product from one phase to another, we have only considered products that we could track in the IMS database from one year to the other, matching products by the reported “preferred name”. Apparently there is a small number of products for which the preferred name has changed over time and we could therefore not track them during the whole five-year period. Consequently, these products are not considered in our probability calculations, which explains why the total number of products in each phase differs between our transition probability calculations set out below and the number of products in a specific phase in Table 2 above. Table 8 sets out the results of our transition probabilities calculations in 1999 to 2000.³⁶ This calculation was repeated for each of the four years.

Table 8: Probability of getting through a phase (1999-2000)

1999_Latest Phase	in 1999	Preclinical	Phase I	Phase II	Phase III	Pre-registration	Registered	Marketed	Suspended	Withdrawn	Discontinued
Preclinical	1229	89%	3%	2%	0%	0%	0%	0%	1%	0%	4%
Phase I	358	4%	76%	10%	1%	0%	0%	0%	0%	0%	8%
Phase II	457	2%	2%	79%	6%	0%	0%	1%	2%	0%	8%
Phase III	211	4%	2%	1%	67%	9%	2%	5%	2%	0%	7%
Pre-registration	109	4%	2%	0%	5%	50%	6%	26%	2%	0%	6%
Registered	46	0%	0%	0%	2%	4%	57%	37%	0%	0%	0%
Marketed	698	0%	0%	0%	1%	1%	1%	97%	0%	0%	1%
Suspended	153	1%	1%	1%	1%	0%	0%	1%	95%	0%	1%
Withdrawn	9	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%
Discontinued	983	1%	1%	1%	0%	0%	0%	1%	0%	0%	96%

Source: CRA calculations based on IMS R&D Focus

³⁶ Note that IMS reports some drugs as being in “clinical”, which can mean that the product is in any of Phase I, II or III. We considered these products, which only account for a small share of total products, in our probability calculations, but do not show them in the tables below. Hence, for some phases the transition probabilities do not add up to 100% but only to 98% or 99%.

Table 9: Average probability of getting through a phase (1999-2003)

Average	Preclinical	Phase I	Phase II	Phase III	Pre-registration	Registered	Marketed	Suspended	Withdrawn	Discontinued
Preclinical	91%	2%	1%	0%	0%	0%	0%	0%	0%	4%
Phase I	4%	73%	13%	1%	0%	0%	0%	1%	0%	8%
Phase II	2%	2%	81%	5%	0%	0%	1%	1%	0%	8%
Phase III	3%	1%	3%	69%	8%	2%	6%	1%	0%	6%
Pre-registration	3%	1%	1%	4%	49%	8%	26%	0%	0%	7%
Registered	0%	0%	0%	2%	4%	44%	46%	0%	0%	3%
Marketed	3%	0%	0%	1%	0%	0%	97%	0%	0%	1%
Suspended	3%	1%	1%	0%	0%	0%	0%	93%	0%	2%
Withdrawn	0%	0%	2%	0%	0%	2%	0%	0%	96%	0%
Discontinued	1%	1%	1%	0%	0%	0%	1%	0%	0%	96%

Source: CRA calculations based on IMS R&D Focus

Table 9 sets out the average probabilities over the four years of data.

CRA forecast of new product authorisations

To derive CRA forecasts of the number of authorisations, we use the transition probabilities derived above to forecast the number of new authorised products for 2004-2008 according to the following methodology:

- Use the number of products reported in each phase in 2003 and the probabilities of transition from 2002 to 2003 to estimate the number of products in each phase in 2004. Applying the transition probabilities from 2002 to 2003 to these numbers yields the estimated number of products per phase in 2005. This step is repeated until arriving at the number of products per phase in 2008.³⁷
- On the basis of the total number of products per phase from 2004 until 2008, we determine the number of new authorised products by counting all products that are reported as registered for the first time in a specific year and all products that are reported as marketed for the first time in a respective year and were not reported as registered in the previous year (assuming that all products that jumped from earlier phases to marketed in a given year received marketing authorisation in the same year).
- We tracked products in the IMS database through the various years by preferred product name and, as explained above, not all products are covered by this matching method. Hence, between 1999 and 2003, we found a certain number of products in all phases each year that we could not track to any phase in the previous year. The

³⁷ There is an argument that success rates will increase dramatically due to biotechnology. J.P. Morgan pharmaceutical analyst Alex Zisson predicts that the specialized genetically tailored drugs developed by biotech companies have a greater likelihood of making it to the market than chemically-derived drugs.

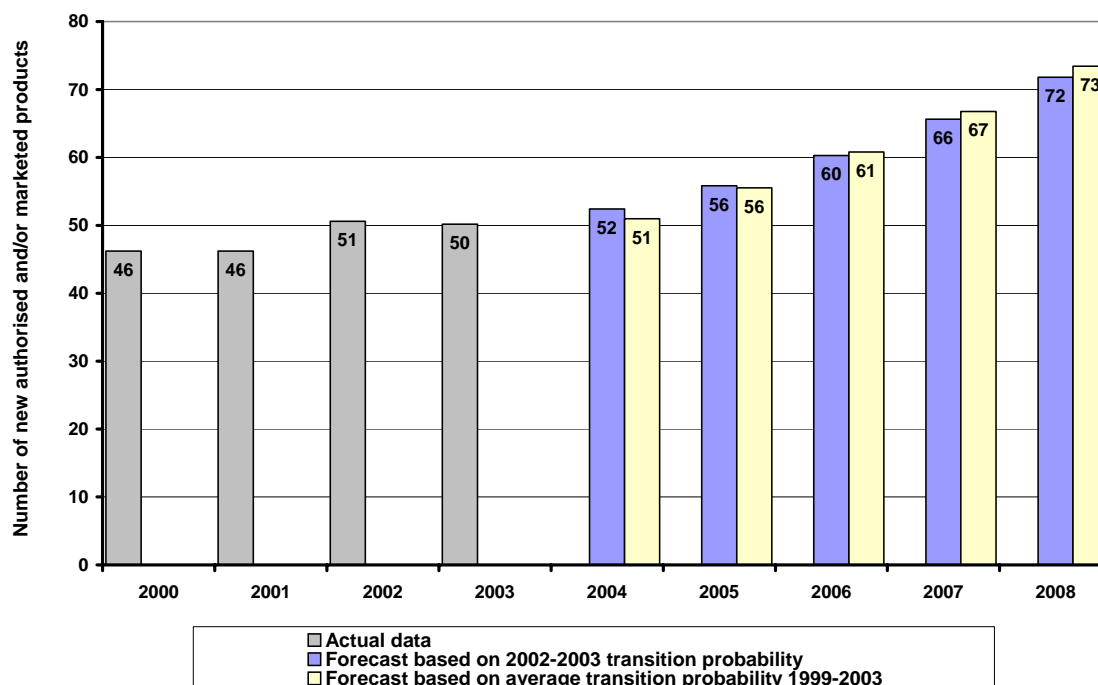
number of “new products” was on average 10% of total products per year. In order to account for these products, we add 10% of total products in each year from 2004 until 2008, allocating the products to the different phases according to their average distribution between 1999 and 2003.

- In our analysis of the IMS data, we searched for products that were in some development phase in Europe during 1999-2003 and grouped them by their “latest phase” as reported by IMS. However, it is important to keep in mind that this does not necessarily mean that all products classed as e.g. “latest phase = phase III” are actually in phase III in Europe. Some of them might be in phase I in Europe and in phase III, their latest phase, in the US. In order to resolve this, we apply a “European adjustment” to our estimated number of new authorised products, based on the share of products that IMS reports as being marketed or registered during 1999-2003 and that actually were marketed or registered in Europe during these years. This share averaged 44% between 1999 and 2003 and the total number of estimated product authorisations is adjusted accordingly.
- We repeat all steps set out above using not the transition probability between 2002 and 2003, but the average transition probability between phases during 1999-2003. This yields the second series set out in Table 10 and Figure 30 below.

Table 10: CRA forecast of number of new authorised and/or marketed products in Europe

	2000	2001	2002	2003	2004	2005	2006	2007	2008
<i>Actual data</i>	46	46	51	50					
<i>Forecast based on 2002-2003 transition probability</i>					52	56	60	66	72
<i>Forecast based on average transition probability 1999-2003</i>					51	56	61	67	73

Source: CRA calculations based on IMS R&D Focus data.

Figure 30: CRA forecast of number of new authorised and/or marketed products in Europe

Source: CRA calculation based on IMS R&D Focus data.

In 2004, the CRA forecast of new (registered and/or marketed) products in Europe is broadly in line with the number of past authorisations issued under the centralised and the mutual recognition procedures over the last couple of years. Still, the most obvious observation when looking at the CRA forecast, which is likely to be an upper bound, is that as of 2004, we estimate a significant increase in the number of new product registrations and launches per year compared to the period from 1999 until 2003. By 2008, the number of new products will have increased by 45% compared to 2003.

Interestingly, our forecast is similar when using the 2002-2003 transition probability and the average probability between 1999 and 2003, which indicates that 2002-2003 was not an unusual year with regard to product authorisations and launches. Therefore this suggests that within the five year window considered for this project, the probability of moving from one phase to another has not changed significantly.

4.2.2 COMPARISON TO EXTERNAL REFERENCE POINTS

The approach above gives a simple and transparent method for forecasting future drug applications and approvals (but clearly makes a significant assumption regarding the probability of transition). However, there exist various other sources of forecasts of future product authorisations in Europe. Clearly, there is already a significant amount of effort

expended on forecasting new products by the companies themselves and by investment analysts.

The most obvious comparator is the launch data suggested by the companies themselves and reported in IMS R&D Focus. Table 11 sets out these forecasts, where we have launch dates (from contemporaneous forecast record by IMS).

Table 11: Launch dates reported to IMS (forecasts made in particular years)

Year	Launches predicted for specific year in 1999	Launches predicted for specific year in 2000	Launches predicted for specific year in 2001	Launches predicted for specific year in 2002	Launches predicted for specific year in 2003
1999	22				
2000	29	16			
2001	14	36	31		
2002	11	20	28	29	
2003	15	20	24	35	34
2004	11	17	21	21	28
2005	5	16	25	25	33
2006	2	7	9	23	16
2007		3	5	9	18
2008		1	1	1	3

Source: IMS R&D Focus

Although it is clear that products are more likely to have a launch date the closer they are to be due to launch – and hence it is inevitable that this forecast will go down over time - it is also telling that this predicts the number of products predicted to launch in 2004 is less than in 2005.

To get a more comprehensive assessment we have looked at analyst reports. Lehman Brothers' PharmaPipelines 2003 is often cited as the best example of an investment analysts forecast of future products. It estimates the number of product launches of companies included in the Lehman Brothers coverage (currently 82 companies globally) until 2008.³⁸ Lehman's total forecast is derived by summing for each individual company the number of drug launches based on the first launch for each product in any region and any indication. Additional indications are not counted as new launches, and co-promotion arrangements are counted as only one product. Lehman provides the estimated total number of product launches and a probability adjusted forecast that takes into account that not all products are expected to be launched with 100% certainty. Hence, the probability-adjusted forecast

³⁸ Note that the number of launches does not necessarily have to be identical to the number of authorised products as there might be some delay between authorisation and actual launch of a product.

should provide a better indicator of the number of launches we can expect to materialise in the future.

According to Lehman Brothers, some small numerical changes in the level of forecasted launches can be due to a change in coverage or the loss of companies or products following acquisitions by companies outside the Lehman universe. Still, Lehman's overall conclusion is that in the next four years, there will be fewer product launches from companies in the Lehman universe than were observed in the last four years (decrease in the average number of product launches per year from 59 to 50). According to Lehman, "[s]ome of this drop may be explained by a lack of visibility of future launches".³⁹

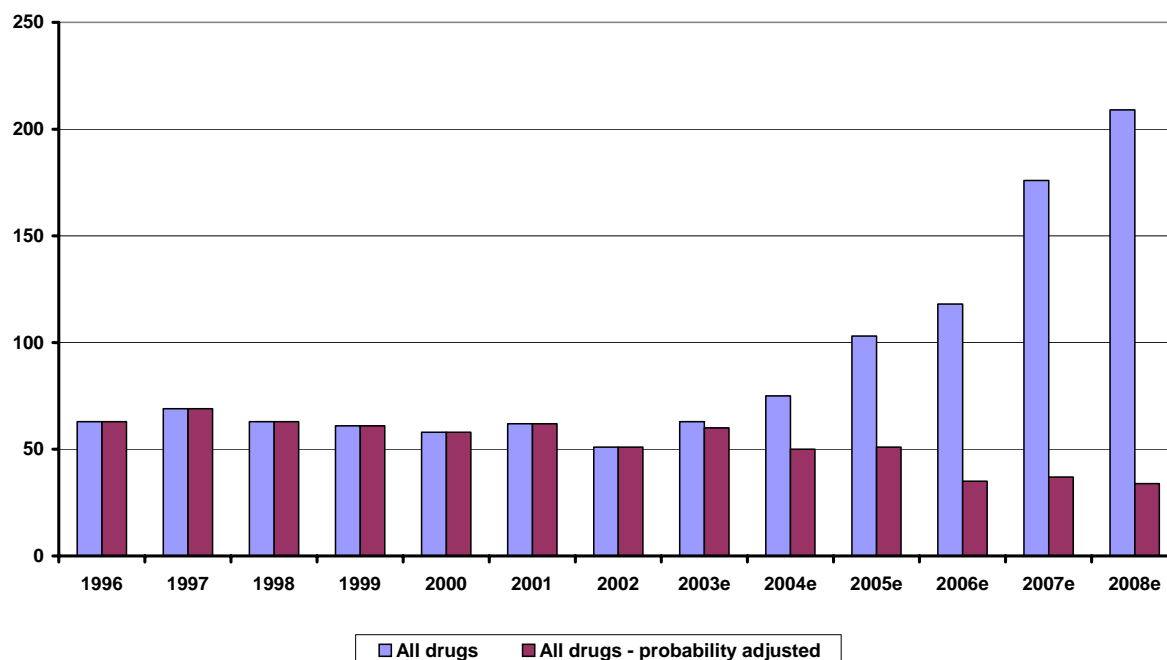
Table 12 shows that Lehman expects the number of product launches to remain relatively stable between 2004 and 2005, similar to the number of new products predicted by CRA. However, contrary to CRA's forecast, Lehman estimates that launches of new products will fall significantly – by 30% – between 2005 and 2006. Product launches are then expected to remain relatively close to this lower level until the end of the forecast period in 2008 (increase by almost 6% in 2007 followed by a decrease by 8% in 2008).

Table 12: Lehman Brothers estimate of number of product launches by year (Oct 2003 analysis)

	1996	1997	1998	1999	2000	2001	2002	2003 e	2004 e	2005 e	2006 e	2007 e	2008 e	Avg p.a. 1998 -02	Avg p.a. 2002 -06
All drugs	63	69	63	61	58	62	51	63	75	103	118	176	209	59	82
All drugs – probability adjusted	63	69	63	61	58	62	51	60	50	51	35	37	34	59	50

Source: Lehman Brothers, *PharmaPipelines 2003*, p.55.

³⁹ Lehman Brothers, *PharmaPipelines 2003*, p.57.

Figure 31: Lehman Brothers forecast of number of drugs launched

Source: Lehman Brothers, *PharmaPipelines* 2003, p.55.

Lehman also provides forecasts of the value of launched products. They expect a higher number of launches with potential of more than US\$500 million, but at the same time an average level of peak sales at around US\$500 million, which might indicate a shift in portfolio mix from mass-market GP products to biological products with a more targeted patient base and lower peak sales potential. Still, the net present value (NPV) per drug may still be high compared to other products. In its analysis of the R&D portfolio of a core group of companies, Lehman finds that the average NPV per R&D project has decreased in recent years, which might reflect a reduction in R&D productivity.⁴⁰

In both cases, expected launch dates reported by companies to IMS and Lehman Brothers's forecasts, one should keep in mind that the respective numbers refer to expected product. The forecast based on expected launch dates reported by companies to IMS has another weakness: IMS does not provide an expected launch date for all products, but only for a limited range. The difficulty for companies to predict the launch of products that are still in an early phase of development may explain why the number of expected launched decreases so dramatically after 2005.

Therefore, based on industry expectations, it must be the case there is an expectation that products will stay in phases longer than has historically been the case, lowering the probability of a product moving from one phase to another in a particular year.

⁴⁰ Lehman Brothers, *PharmaPipelines* 2003, pp.55-57.

4.3 New technologies

The European Commission identified four technologies that we need to account for in our assessment:

- Gene therapy;
- Cell therapy;
- Tissue engineering; and
- Pharmacogenomics.

Below we use gene therapy as a case study to see if it is already allowed for in the methodology above and whether there are wider implications for our analysis.

4.3.1 A CASE STUDY OF GENE THERAPY

Gene therapy is the technique for correcting defective genes by the transfer of corrective genetic material into a patient's cells to replace or alter a specific dysfunctional gene. There are a number of approaches currently being investigated:⁴¹

- The most common approach is inserting a normal gene into a nonspecific location within the genome to replace a nonfunctional gene;
- An abnormal gene could be swapped for a normal gene through homologous recombination;
- The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function; and
- The regulation (the degree to which a gene is turned on or off) of a particular gene could be altered.

The EC (based on an evaluation of the EMEA) and the Food and Drug Administration (FDA)⁴² have not yet approved any human gene therapy product for sale. The state of technology is still said to be “experimental” and the progress has been disrupted by problems with clinical trials.

⁴¹ Based on a description of gene therapy:

http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml

⁴² The first commercial launch of a gene therapy looks set to go ahead in China in January was recently reported in Scrip. The treatment, for head and neck squamous cell carcinoma (HNSCC), uses an adenoviral vector to deliver the human p53 tumour suppressor gene. The product, Gendicine, has been developed by SiBiono (Saibainuo) Gene Technologies, a gene therapy venture based in Shenzhen, Guangdong province. It was licensed for marketing by China's State FDA in mid-October, the first such clearance worldwide for any gene therapy (Scrip No 2900, p 22).

The first gene therapy clinical trials began in 1990. They were however to suffer a significant setback when, in 1999, one of the participants in a gene therapy trial for ornithine transcarboxylase deficiency (OTCD) died. It was believed that his death, from multiple organ failure, had been triggered by a severe immune response to the adenovirus carrier.

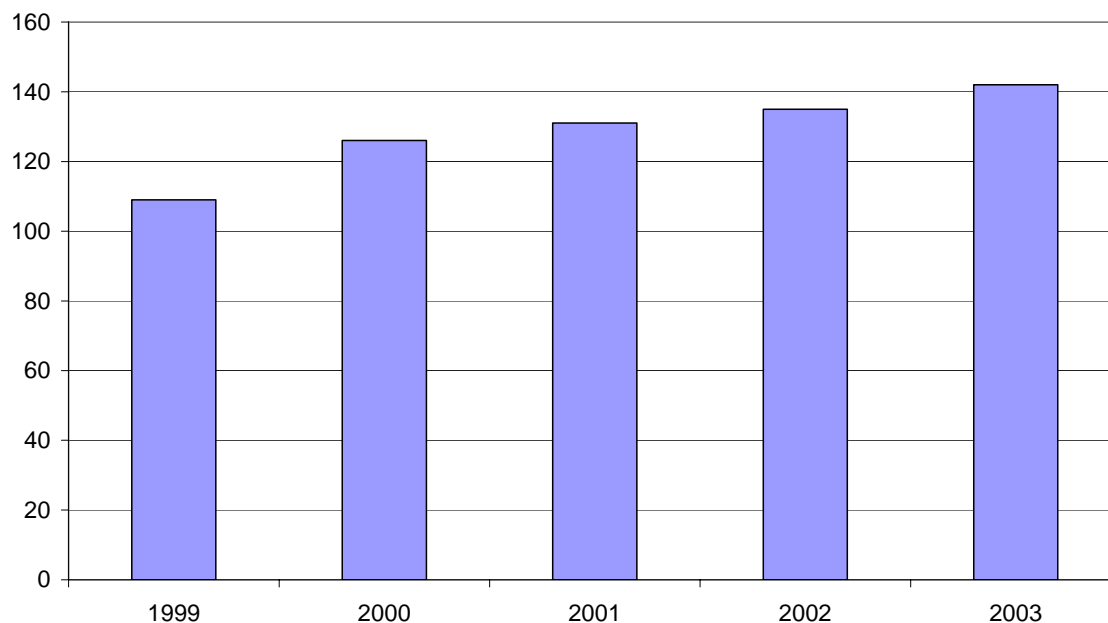
Another major blow came in January 2003, when the FDA placed a temporary halt on all gene therapy trials using retroviral vectors in blood stem cells. FDA took this action after it learned that a second child treated in a French gene therapy trial had developed a leukemia-like condition. Both this child and another who had developed a similar condition in August 2002 had been successfully treated by gene therapy for X-linked severe combined immunodeficiency disease (X-SCID), also known as "bubble baby syndrome." This was followed by temporary delays in the on-going trials in the France and the UK (although the UK trials are now on-going).

However, even with these setbacks, the applications of gene therapy used in combination with bone marrow transplantation represent the most tangible success for gene therapy to date. A number of characteristics need to be taken into account:

- Products are made in house by non-profit making organisations – this is not currently a commercial operation – and is aiming at extremely rare genetic conditions;
- The use of gene therapy in bone marrow represents an “easier” application of gene therapy but even then it has been 10 years in development, so development times are still likely to be substantial in the future;
- The applicability is small with each case assessed on its own merits and only approximately 20 cases treated so far.

However, beyond this modest application, there is considerable research effort into the more speculative applications of gene therapy to cancer and cardiovascular disease. More recently, commercial gene therapy products have finally reached the later stages of clinical trials. A number of key projects are in Phase III trials and the first regulatory submissions are anticipated in the next 3 years. Almost all of the gene therapies currently in Phase III clinical trials are indicated for cancer.

Currently, there are over 200 gene therapy products in development covering several therapeutic areas. To get a measure for the prospects of gene therapy products, we ran a text search on IMS's R&D Focus database, which provides a measure of the number of products in development. Although this will not pick up every product, it will give a directional indicator on progress.

Figure 32: Gene therapy products in R&D Focus (1999-2003)

Source: IMS R&D Focus and CRA analysis

As can be seen from Figure 32, the prospect for applications for new active substances arising from gene therapy products is growing, with the number of products in development growing at 7% a year. However, to date there is no evidence of imminent applications.

Table 13 shows where products currently stand in terms of their latest phase of development. Although there are four products in phase III development, gene therapy is unlikely to represent more than a handful of applications in our five-year horizon.

Table 13: Gene therapy products by phase (2003)

Phase	Number of products
Preclinical	83
Phase I	15
Phase II	14
Phase III	4
Pre-registration	0
Registered	0
Marketed	0

Source: R&D Focus and CRA calculations

Current obstacles to gene therapy development are said to be mainly gene delivery but non-clinical factors include costs associated with gene therapy development and an uncertain regulatory environment are also thought to be important.

5 Overall assessment of Phase I

Our analysis of the evidence regarding innovative activity over the last five years supports the following conclusions:

Pharma industry R&D expenditures - *Prima Facie* the evidence of the trends in global R&D expenditure over the past decade shows a strong upward trend, which has continued in recent years. There is also a clear trend with a higher proportion of R&D expenditure being spent in the US at the expense of Europe and Japan. However, even allowing for this, R&D expenditure in Europe has continued to grow significantly.

R&D output in terms new compounds in preclinical development – There is rapid growth in the number of compounds being investigated but this is not currently translating into the same strong growth in the number of products entering into clinical development. In the US, this is currently stable, there is a strong decline in Japan.

R&D output in terms of compounds in clinical development – Analysis based upon IMS data for products in development in Europe shows that this picture varies depending on the stage of development. There is a substantial increase in the early phases of development (in particular, Phase II). Based upon our analysis so far this may reflect the fact that a new wave of patented inventions is coming through from fundamental advances in the biosciences and medicine. What is less clear is whether the lack of increase in late stage development projects indicates just a time delay effect in the new bio based products reaching that stage, or that more severe criteria based upon market pressures are being applied to putting candidate products into the expensive clinical phases, resulting in higher attrition rates in making the transition and in the same number of new drugs coming through development as before.

R&D output in terms of licensed products - Both EMEA and FDA data show a decline in applications leading to a reduction in authorisations in 2001 and 2002 but a recovery in applications in the last year. This should result in an increase in authorisations next year. Extrapolating the trend over the last three years would therefore yield an overly negative assessment of future authorisations. Looking at this from a longer-term perspective (which is only possible using the US experience) suggests we should not be concerned about this recent reduction, given the level of volatility experienced in the past.

R&D output in terms of types of products - In the US there is a higher proportion of new biologic products coming onto the market, in Europe, based on partial data, this does not appear to be the case, at least not for products authorised under the mutual recognition procedure.

Equally, the introduction of an Orphan drug designation in Europe has led to an increasing proportion having this designation. Given the relative stability of number of drugs going

through the US Orphan drug designation and the downturn in applications, we believe it is likely that the share of European authorisation assigned as Orphan drugs is likely to converge over the medium term. We therefore anticipate this is likely to reach a level similar to that experienced in the US.

In terms of therapeutic value, we have not found a European source of data that allows us to make a meaningful comparison of this kind. Analysis based on data from the FDA, suggests a shift in the mix of products approved. In recent years the proportion of the total number of applications that result in a NME appears to be somewhat lower and the number of products going through the priority channel has fallen as well. However, although this is the ‘best’ measure of therapeutic value available it is by no means ideal. In particular, it excludes the increasing number of biological drugs. Therefore, although there is a cause for concern, the jury is still out on whether the social value of new products is falling.

R&D output in terms of commercialized products – Evidence based on the probability a product moves from development to an application, application to authorisation, or registration to marketed suggest that this relationship is relatively constant over the last five years in Europe. There is therefore no evidence that drug manufacturers are better at assessing whether a product is worth marketing prior to registration or that the regulatory environment has resulted in more withdrawals or negative opinions. There is little evidence that the fall in products reflects better assessment of commercial success or harsher regulatory decisions. This does not preclude that the number of products have been withdrawn at an earlier stage due to the expense of the regulatory process or expectations that the product would get a negative opinion.

Equally, evidence from analysts’ reports suggests that there has been little change in the predicted distribution of peak sales over the last five years at a global level. This is in sharp contrast to the five years preceding this, which saw a concentration of effort on blockbuster products.

Assessment of the future path of applications, authorizations and commercialised products – Using the analysis described above we are able to look to the next five years in Europe. Based on an assessment of products in the pipeline, we can predict how many products will move from phase to phase and enter into the registration process. This suggests that based on historical probabilities there will be a gradual increase over the next couple of years. Other forecasts are less optimistic. However, overall our assessment is that the recent downturn does not reflect a trend.

New technologies – However, it is also clear that new technologies offer the opportunity for future growth. Within our data we can identify many new technologies, such as gene therapy, and see that these contribute to the growth in products in early stages of development. However, we can only observe these products in any numbers in Phases I to II. Therefore, it is unlikely that these products will contribute a significant number of applications or authorizations over the next five years. This is made more complicated,

however, by evidence that these products have significantly different probabilities of success. However, this supports that the level of applications and authorisations will at least return to the long-term average.

Overall assessment: Although, we do not believe that the recent fall in applications and authorisations reflect a crisis in innovation, there are clearly issues with respect to getting new drugs through development, bottlenecks in drugs in different stages of development and possibly in the types of drug being developed.

6 Phase II: Causal factors underlying innovation in the pharmaceutical industry

In Phase I of our study, we found that there are areas of concern regarding the current state of innovation, in particular:

- There has been a small reduction in the number of authorisations but it is predicted that this will be followed by a recovery over the next 2-3 years;
- Of more concern, there is an increase in costs of R&D with little resultant increase in the number of new products;
- There is concern regarding the quality of products in terms of therapeutic value (however there is only weak evidence that it has fallen);
- Regarding the European industry, there is concern about relocation of R&D to the US at the expense of Europe.

Building on our findings of Phase I, the purpose of Phase II of this report is to understand the range of causal factors and present an assessment of the degree to which they were responsible for the observed changes in innovative behaviour. In Phase III of the report, we will then consider whether there are implications for regulatory intervention or whether product manufacturers need to change their behaviour.

6.1 A very simple model of innovation

Although there are complex models looking at how different factors interact to encourage innovation we adopt a very simple model of innovation: firms compete through investing in R&D to win the race to discover new products at which point they can earn profits yielding them a return on their investment. To investigate the causal factors behind the changes in innovative behaviour identified in Phase I, we investigate three sets of relationships:

- Changes in the costs of research and development – if the costs of innovation fall (through technological progress for example – often referred to a “push” factors), we would expect an increase in the incentives to innovate;
- Changes in the returns to research and development (the regulatory/reimbursement system, for example, often described a “pull” factors) – if the returns to innovation fall we would expect a reduction in the incentive to innovate; and,

- Changes in the nature of competition between pharmaceutical companies – in this case the result is more complicated with the implications for the incentive to innovate depending on the nature of competition.

In each of these cases, we seek to identify the underlying drivers of the change in order to determine whether it results from evolution of the industry or actions by the regulators/payers. This will be used in Phase III of this report, which will consider whether there is a case for intervention and the priority for action.

7 Phase II: The cost of research and development

As is shown in Table 14 below, there have been many attempts to estimate the cost of bringing a new product to market. The most recent study by Tufts has estimated costs in the US of almost \$900 million for successfully bringing a product to market.⁴³

Table 14: Comparison of cost estimates

Source	Date	Estimate	Details of the estimate
Tufts Centre for the study of drug development (CSDD)	May 2003	\$897 million (2000\$)	Incorporates post-approval costs to Nov 2001 estimate of \$802 million
Tufts CSDD	Nov 2001	\$802 million (2000\$)	Fully capitalized costs including the costs of failure based on analysis of 68 randomly chosen drugs
Boston Consulting Group	Nov 2001	\$880 million (2001\$)	
Public Citizen	2001	\$341 million (2000\$ pre-tax)	Based on adjusting the Tufts analysis
Boston Consulting Group	1990s	\$350- \$500 million (1990\$)	Increase from 1980-83 estimate to that in early 1990s
Lehman Brothers	1996	\$608 million (1996\$)	"guide to future development costs if the process is started today"
US Office of Technology Assessment (OTA)	1994	\$400 million (1994\$)	Using DiMasi results but with a higher discount rate
US OTA	1992	\$259 million (1990\$)	Based on adjusting 1990 estimate of \$231 million for inflation using GNP implicit price deflator
Tufts CSDD	1987	\$231 million (1987 \$)	Based on 93 NMES entering development in 1970-1982

Source: Parexel (2003).

Table 14 supports the argument that costs have increased from the mid 1980s to the 1990s. There is still, however, considerable debate as to the appropriate methodology. It is generally accepted that it should include: the cost of pre-clinical and clinical trials, and the costs of failed products. There is considerably more debate over:

- The need to allow for the opportunity cost to take into account the time between investment and reward;
- The allowance for a corporate tax rate – as R&D is a cost it is tax deductible; and
- Adjusting for Government investment in new product development where they have paid for some development costs.

⁴³ Tufts Center for the Study of Drug Development (2003).

In particular, there was a vigorous debate in the US between the consumer group, Public Citizen⁴⁴, and the Tufts group about whether the Tufts estimate was overstated, due to a biased treatment of the above factors. Although on the face of it Public Citizen had significant objections, Tufts responded with a strong rebuttal:⁴⁵

- Any investment that takes between 10-12 years before repayment needs to account for the opportunity cost of time;
- Although R&D can be offset against tax, the aim of the study was to look at the resources devoted to developing new products rather than the cost falling onto providers; and
- Although the Tufts 2001 study included only self-originated products this was unlikely to bias the resource cost of bringing products to market.⁴⁶ This did not exclude drugs that had been partly sponsored by Government funds and in any case, Tufts argued that only 3% of drugs were discovered in Government labs.⁴⁷

If we accept the Tufts methodology as the best evidence regarding the cost of research and development, there is strong evidence that the real cost of bringing a new product to market has risen dramatically over the last three decades: \$138 million for products in 1970s, \$318 and \$802 million for drugs in the 1980s and 1990s respectively. Looking at the \$802 million in more detail, out of pocket costs (that is direct costs related to the successful product) are dominated by the cost of clinical trials, but once we have taken into account the opportunity cost of time, preclinical trials account for 41% of total costs:

Table 15: Decomposition of the cost of developing a new drug (2000\$)

	Out of pocket expenditures	Including cost of capital
Preclinical	\$121	\$336
Clinical	\$282	\$466
Total	\$403	\$802

Source: Tufts Centre for the Study of Drug Development.

Looking at the changing cost structure between the Tufts estimates (as set out in Table 16) we find that costs have risen in real terms for both clinical and preclinical trials.

⁴⁴ Public Citizen (2001).

⁴⁵ Tufts Center for the Study of Drug Development (2002).

⁴⁶ If we assuming a competitive market for in-licensing there is unlikely to be a substantial difference between the total costs of developing a product internally or one that has been licensed in.

⁴⁷ In an analysis by Ernst and Young for PhRMA they also found that Public Citizen had incorrectly concluded that Tufts had included marketing costs and assumed that me-too products were less risky than innovator products. (See Ernst & Young LLP (2001)).

Table 16: Change in the end value of costs of development (2000\$)

	Hansen (1979)	DiMasi (1991)	Tufts (2001)
Preclinical	84	214	335
Clinical	54	104	467
Total	138	318	802

Source: DiMasi, Hansen, and Grabowski (2003).

However, the cost increases were higher for the clinical periods, with an increase 5 times that of preclinical costs. Looking at the relative cost between phases we find that:

- Phase III cost to Phase I was 6.0 in previous study, this was 5.7 in most recent study;
- Phase II cost to Phase I was 1.9 in previous study, this was 1.5 in most recent study.⁴⁸

The changing attrition rates (the probability that a product fails a particular phase of development) amplify this effect.⁴⁹ The earlier study 1991 analysis had similar overall success rates but products were kept in development for longer. That is, the 2001 Tufts study found higher attrition rates for the earlier phases. If we were to hold the attrition rates the same, today's cost would be higher still.

Table 17: Change in capitalised costs of development (2000\$)

	Mean Cost (2000) in millions of dollars	Probability of Entering Phase (Old)	Probability of Entering Phase (New)	Expected Cost (Old)	Expected Cost (New)
Phase I	15.2	100.0%	100.0%	15.2	15.2
Phase II	23.5	75.0%	71.0%	17.6	16.7
Phase III	86.3	36.3%	31.4%	31.3	27.1
Long-Term Animal	5.2	56.1%	31.4%	2.9	1.6
Total				67.1	60.6

Source: Tufts Centre for the Study of Drug Development and CRA analysis.

Interestingly the authors found that products that were perceived as having a higher therapeutic value, through going via the priority channel, also had higher costs. As the authors note, this could reflect that it is worth spending more on a priority product or that it costs more to get it successfully through to launch.

⁴⁸ DiMasi, Hansen, and Grabowski (2003).

⁴⁹ In 2001, the probability of reaching phases II and III was 71 percent and 31.4 percent, respectively. In 1987, the probability of reaching phases II and III was 75 and 36.3 percent, respectively. (See DiMasi, Hansen, and Grabowski (2003)).

7.1 Reasons for rising costs

There is therefore clear evidence that the costs of developing a product have risen over the last three decades. The authors of these studies, in particular DiMasi, attributes the increase in total cost beyond inflation to rising costs of clinical trials: “The difficulty in recruiting patients into clinical trials in an era when drug development programs are expanding, and the increased focus on developing drugs to treat chronic and degenerative diseases, has added significantly to clinical costs.”⁵⁰ Below we test a number of hypotheses:

- Whether the complexity of products has risen leading inevitably to higher research and development costs;
- Whether there has been an increase in the size of clinical trials;
- Whether this has been caused by increasing regulatory requirements;
- The impact of the authorisation process; and
- The impact of new technologies.

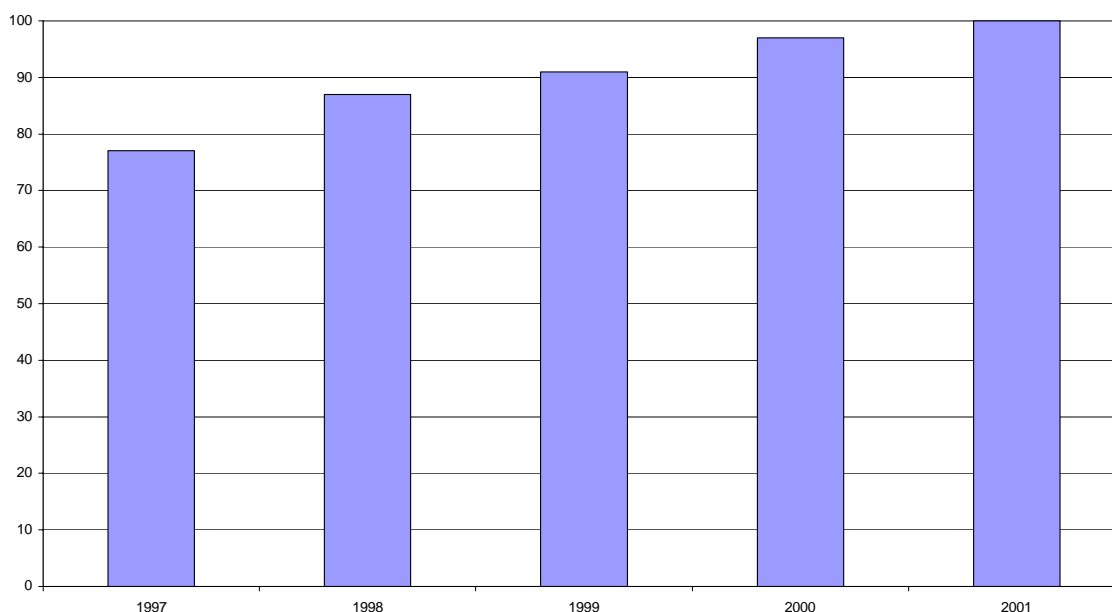
We then look at whether there are regional trends that might explain the relocation of R&D that we observed in the Phase I analysis.

7.1.1 COMPLEXITY OF THERAPEUTIC GROUPS UNDER DEVELOPMENT

PhRMA attributes increasing R&D costs to the long process (10 to 15 years) and the growing complexity of targeted diseases.⁵¹ That is, they argue that the easier products have been developed; we are now developing more complex products to meet the needs of more complex diseases. Looking at the average cost of a patient trial across all therapeutic areas it is clear that the cost has risen. This provides circumstantial support for this hypothesis.

⁵⁰ Tufts Center for the Study of Drug Development (2001).

⁵¹ “2004 Industry Profile,” available at www.phrma.org.

Figure 33: Index of mean cost per patient trials by year (Phase I-IV), 1997-2002

Source: DataEdge 2003

To understand this trend there has been considerable research into how R&D costs vary by product type. The most recent 2004 Tufts CSDD study⁵² found that therapeutic class is a critical determinant of drug development cost. The study examined four drug categories: analgesic/anaesthetic, anti-infective, cardiovascular, and central nervous system (CNS). Analgesic/anaesthetic drugs were the least costly to develop, requiring an average of \$375 million for total out of pocket and time costs compared to the average \$466 million for all drugs, and they took 61.8 months for clinical and approval phases compared to the average of 90.3 for all drugs. The most expensive category of drugs was CNS drugs, which cost an average of \$527 million and required an average of 114.6 months for clinical and approval phases. The figures do not include non-clinical research and development costs. There are clearly, therefore, significant cost differences between therapeutic categories.

Danzon, et. al⁵³, examined the extent to which development success varies across therapeutic categories. Drugs for respiratory indications had the lowest predicted probability of being approved, whereas hormone preparations had the highest predicted probability. This study differed from DiMasi's in that DiMasi identified the therapeutic category based on the first indication for an NCE while Danzon et al based it on a specific indication or condition. Danzon's found a higher overall predicted probability because most firms test for many indications and therefore have higher success probabilities. Indications targeting large categories (respiratory therapy, central nervous system, alimentary and cardiovascular) had

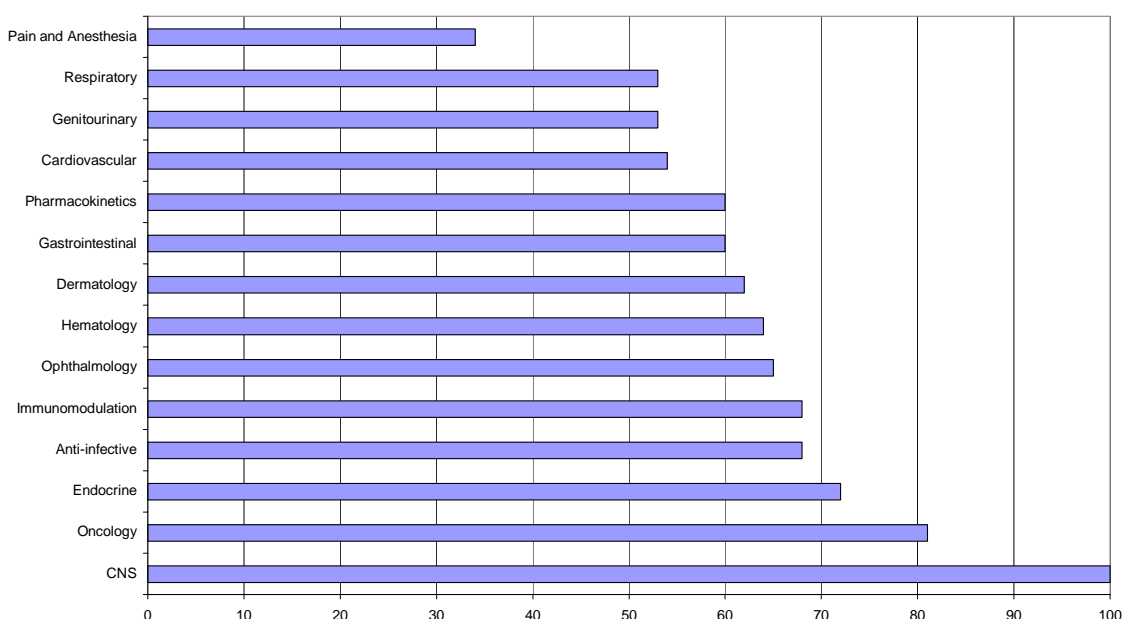
⁵² Tufts Center for the Study of Drug Development (2004).

⁵³ Danzon, Nicholson, and Sousa Pereira (2003).

lower predicted success probabilities, but they concluded that firms appear willing to develop these drugs because they have greater sales potential.

The following shows the magnitude of differences in clinical trial costs per patient by therapeutic area and again supports the high cost of CNS products versus products in the respiratory area:

Figure 34: Index of mean cost per patient trials by therapeutic area (Phase I-IV), 1997-2002⁵⁴



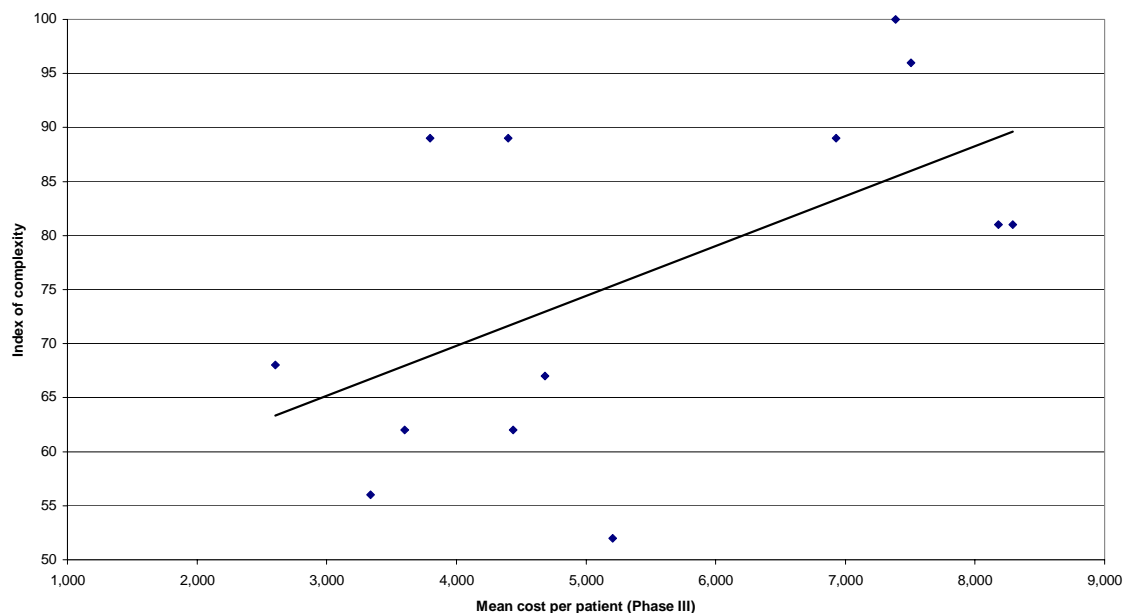
Source: DataEdge 2003

According to Figure 34 the cost of undertaking patient trials for a new CNS product is twice as high as for a respiratory product or a cardiovascular product. However, the bulk of therapeutic areas have a similar mean cost per patient trial.

Looking at the complexities of different therapeutic areas, there is a clear relationship between complexity as measured by the number of procedures per patient and the cost of patient trials.

⁵⁴ This is measured by looking at the number of procedure per patient. A procedure refers to an interaction with the patient such as undertaking an ECG for example. Although an imperfect measure of complexity it provides a rough measure of the degree to which patients will require extensive monitoring, titration or check-ups.

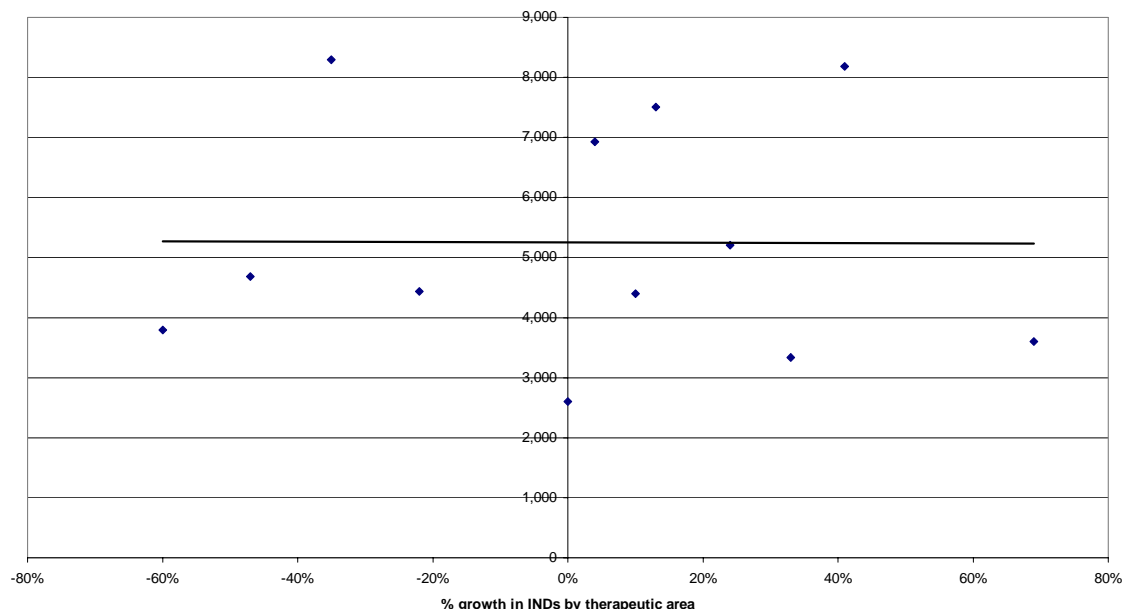
Figure 35: Relationship between measures of complexity and average cost per patient in Phase III Trials



Source: DataEdge 2003

However, it is less clear that there is a strong relationship between the fastest growing therapeutic areas over the last five years, as measured by therapeutic areas with the biggest change in the INDs submissions (CNS, respiratory and pain and anaesthesia) and the therapeutic areas with the highest cost per patient.

Figure 36: Relationship between growth in INDs in therapeutic areas and the cost per patient in Phase III trials



Source: DataEdge 2003

It would appear from this data that there is a danger of focusing too heavily on a single therapeutic group such as CNS, where it is clear that there has been strong growth and costs appear unusually high, and losing the bigger picture. The question is therefore whether clinical trial sizes have increased and why.

7.1.2 LARGER TRIALS

There is strong anecdotal evidence that the size of trials is much greater than in the past, pushing up costs. This is supported by research by Pfizer that found that the typical new drug undergoes more than twice as many clinical trials now then it did in the 1970s.⁵⁵ The number of patients per NDA has increased from a low of 1,321 in the period 1981 – 1984 to 4,237 for the period 1994-1995.

However, there is considerable disagreement as to the reason behind the increase in the number of trials. The increased number of clinical trials is not all attributed to increased requirements from regulatory authorities such as the FDA and EMEA.

⁵⁵ Pfizer (1999).

It is claimed that the testing for new drugs is rising by 12 percent per year, at least in part due to testing for marketing purposes. It is widely acknowledged that there is a significant difference between getting a drug approved and having it be a commercial success.⁵⁶

In particular, companies are doing these tests for marketing reasons (i.e. so that they can demonstrate results relative to other products already on the market – a recent example would be the PROVE IT study that compared the benefits of different statins) and not necessarily for regulatory reasons (i.e. not necessary to get the product authorised).

The tests may not be mandatory, but to be placed on a formulary or to receive favourable pricing, the additional clinical trials are necessary. Companies are investing in clinical trials to convince health maintenance organisations that their drugs should be placed on formulary or to improve market share relative to competitor's products. "Pharmaceutical companies have greatly expanded their clinical testing, often measuring their new products against myriad rivals in hopes of finding incremental differences that will allow them to land a better ad slogan, a broader treatment claim, or a spot on the restricted list of products insurers will reimburse. The number of drug trials has exploded far beyond the dictates of the FDA, which says its requirements haven't grown substantially in recent years."⁵⁷

This appears to be the case in the US, when comparative clinical trials are required to get a good formulary position or in Europe where trials are required to meet the needs of cost-effectiveness reviews and get a higher reimbursed price.

The requirements demanded for pharmaco-economic studies is likely to continue to grow in the future, according to Tufts, as managed care providers, pharmacy benefit managers, and foreign pricing and reimbursement authorities require additional evidence on pharmaceutical value.⁵⁸ Therefore, this would seem to reflect a change in clinical trials to reflect the market conditions for reimbursement rather than simply a cost increase due to more complex products.

Similarly, as manufacturers increasingly pursue the global launch of their pharmaceuticals, they must comply with different regulatory systems and local requirements, e.g. clinical trials based on local populations. In the EU, the centralised procedure has alleviated some of this pressure.

It may also be the case that the sheer number of drugs on the market increases the probability that patients might experience an adverse drug event (ADE). As a result, the data required to demonstrate patient safety will become increasingly complex over time.

⁵⁶ Langreth (1998).

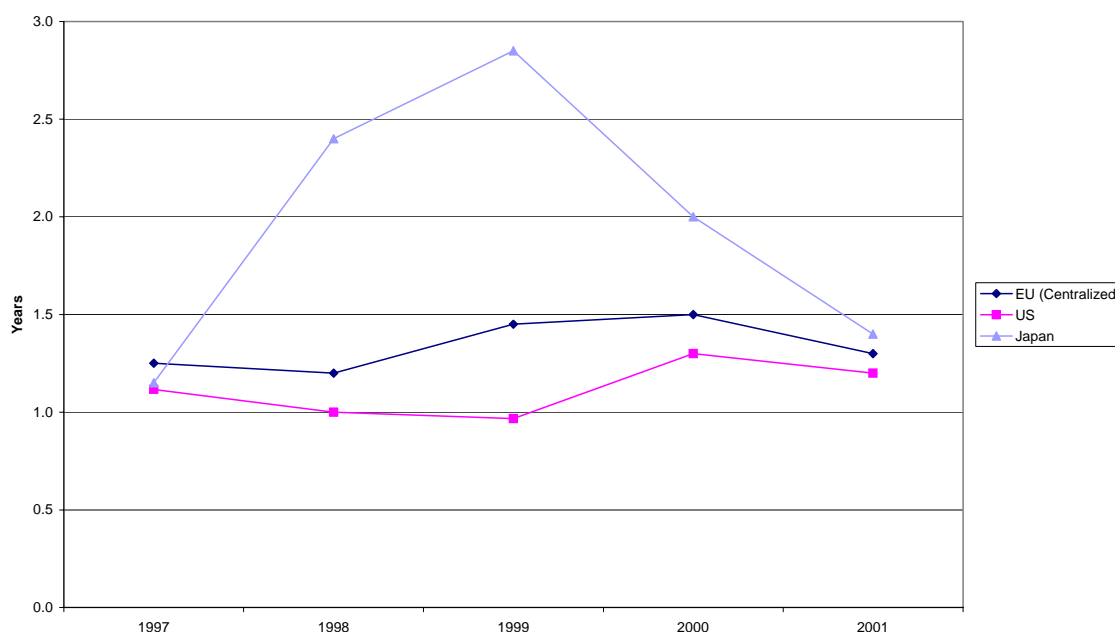
⁵⁷ Langreth (1998).

⁵⁸ Langreth (1998).

7.1.3 REGULATORY REQUIREMENTS

Regulatory authorities influence the R&D process directly during the review process but also indirectly by influencing the types of study undertaken during the development of the product. Looking at the authorisation process there is clear convergence between the European and US authorisations. Figure 37 shows the average regulatory approval time in EU (for the centralised procedure), the US and Japan.

Figure 37: Regulatory approval times 1997-2001



Source: CMR

The industry has also explained the increasing cost of clinical trials by increasing demand from regulators. This has a number of potential dimensions:

- **Improved efficiency:** it appears that the regulatory clinical dossier has been decreasing in length even if it has been increasing in complexity. Evidence from Carl Peck, director of the Georgetown centre for drug development science suggests that converging “scientific objectives, medical imperatives and pharmacoeconomic realities are resulting in increasingly complex development programs”. A CMR survey of 14 leading drug companies found the mean number of trials in 21 marketing dossiers declined from 45 in 1995/1996 to 20 in 1998/1999 although the number of individuals in the studies had not decreased substantially;
- **Reaction to events:** In the 1990s, there were a series of withdrawals of pharmaceuticals from the market. The withdrawals, which included Janssen Pharmaceutical’s Propulsid, Wyeth’s Fen-Phen, Pfizer’s Rezulin and Bayer’s Baycol, led to demands for more complex clinical trials by the FDA. The increased demands

called for more testing for drug-to-drug interaction, potential liver toxicity and for cardiac risk.

- Future standardisation: On July 1, 2003, the Common Technical Document (CTD) was adopted the EU, US, and Japan. The document provides a common information format for regulatory submissions in all three regions, and is required by the EMEA, Japan's MHLW, and Canada's Therapeutic Product Programme, and is "highly recommended" by the FDA. This document is expected to "enhance the quality of regulatory reviews and improve communications between sponsors and regulatory agencies." (Outlook 2003, Tufts)
- Finally, increasingly stringent protocols for patient informed consent and other regulations increase cost per trial patient. As a result, manufacturers must commit an increasing amount of funding to R&D operations for molecules in the latter stages of development that might not be matched by the increasing efficacy of the product.

7.1.4 NEW TECHNOLOGIES

Tufts analysed 12 new biopharmaceuticals products that were approved between 1994 and 2000 and compared them to NCEs that were approved during the same time period.⁵⁹ The study found that, on average, the development of biopharmaceuticals involved significantly fewer studies and clinical subjects per application compared with new chemical entities:⁶⁰

- 63% fewer Phase I trials for orphan products versus non-orphan products; and
- 52% fewer Phase I trials for priority-reviewed products versus products going through the standard review process.

Comparing the size of the clinical trials, by the number of subjects, they found that whereas biopharmaceuticals had 1024 subjects per application, NMEs had over 5000. However due to the difference in patient population and the market size of the resulting products it may be unsurprising that there are currently significant differences in the cost of undertaking clinical trials for pharmaceuticals versus biopharmaceuticals. It is therefore useful to consider the expectations of clinical development costs as genomics increases in importance.

According to the Boston Consulting Group, the implementation of genomics and genetics can increase efficiency (lower cost or higher speed) or reduce failure rates in the future. They find that by applying genomics, companies could on average realize savings of nearly \$300 million and two years per drug based on genomics available today. As technology improves, savings could be even greater. Implementing the new technology, however, will take a few years and may involve an increase in costs as necessary quality controls are established. The BCG model predicts that implementation will increase the cost of quality control by \$200

⁵⁹ Drug Information Journal.

⁶⁰ As the authors themselves acknowledge one reason for this is that these products may be aimed at rare conditions affecting a potentially small number of subjects.

million and add more than one year per drug. This is attributable to the extra time needed to understand target function and develop appropriate assays in target validation and screening.

However, again we find that there is contrary opinion, Lehman Brothers hypothesises that genomics threatens to increase the overall R&D costs and the average cost per NCE. The study found, “despite the current need for better target validation through functional genomics, these technologies are unlikely to add value in the near term. These technologies are simply not yet robust enough to yield truly validated targets.”⁶¹

In a report from February 2001, Lehman Brothers describes the R&D situation as an “expense bubble” that could potentially arise as the use of novel targets leads to higher attrition rates in Phase II trials. This follows from the assumption that new chemistry and biology will necessarily create a higher failure rate until target validation technology catches up with target discovery technology. They argued pharmaceutical companies would enter a “productivity cliff” in the early 2000s, after which productivity will rise. The impact of this will be to raise the cost of developing a new NCE to \$1.6 billion by 2005 (without significant improvements to genomics) or \$1.3 billion with modest technology improvements. Once the fruits of genomics mature, however, they expect the cost per NCE to fall \$600 million by 2010. Therefore, even with genomics, costs do not fall back to the level seen in the 1990s.

7.2 Location of research & development

Given the increasing cost of clinical development it is not surprising that pharmaceutical companies have been looking to reduce these costs by thinking about the location of R&D.

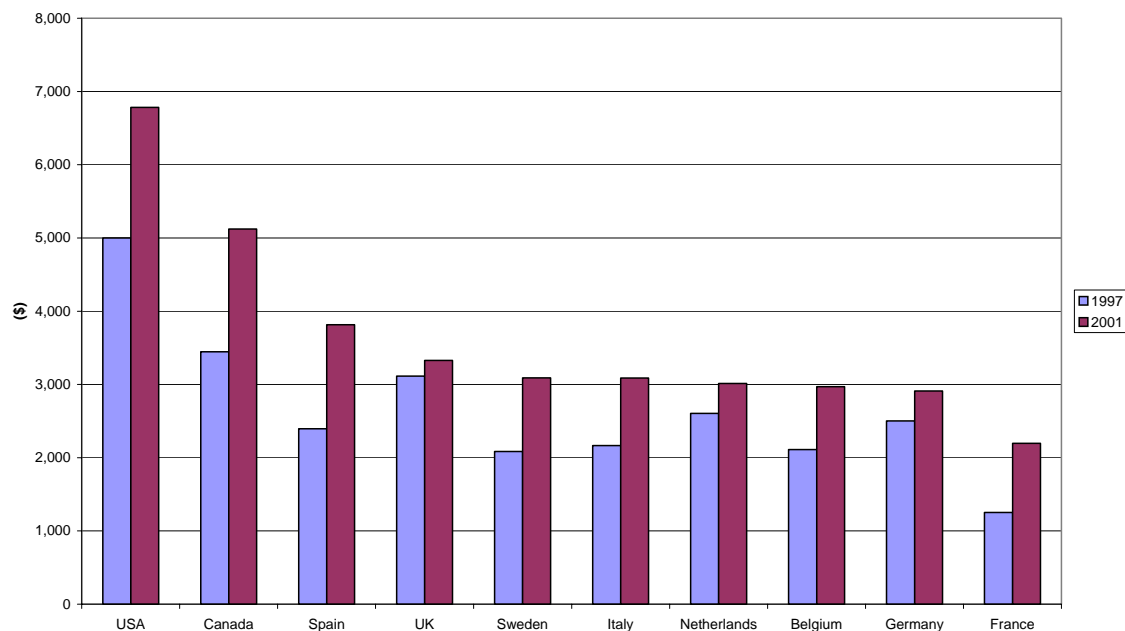
There is increasing interest in the use of lower income countries for R&D activities, especially through the use of contract research organisations. Recent estimates are that the contract research organisation market in Europe is currently \$2.6 billion compared to \$4.18 billion in the US.⁶² The market in Europe is expected to grow to \$4.26 billion by 2007, however, as firms move to Eastern Europe. Eastern European contract research organisations (CROs) have a number of benefits in addition to low cost patient reimbursement. For example, patients in the region tend to be under medicated, reducing the risk of patients using competing medications and compromising the integrity of final data.

At the same time, there is clearly a trend to spending R&D expenditure in the US. As shown in the figure below, this is clearly not a cost issue. The US has the highest mean cost per patient of any of the countries examined.

⁶¹ Lehman Brothers (2001).

⁶² R&D Directions (2004).

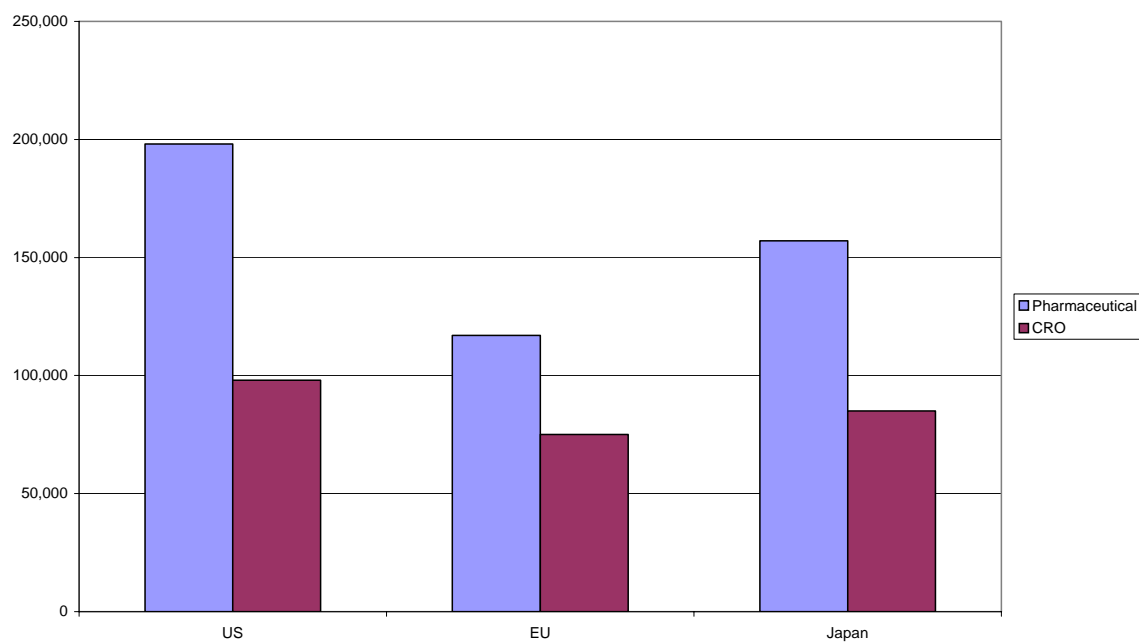
Figure 38: Comparison of clinical trial costs by country (mean cost per patient in phase III clinical trial)



Source: Fast Track Systems, Inc., September 2002

This is verified by information from contract research organisations such as Quintiles.

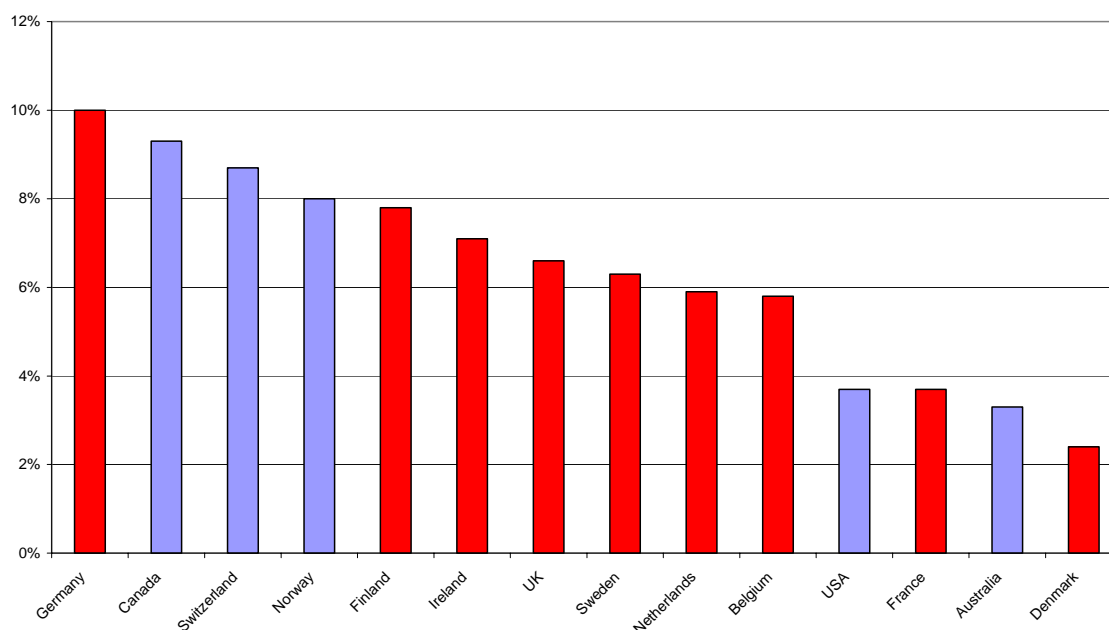
Figure 39: Cost comparison (CRO cost per full-time representative US\$)



Source: Quintiles Transnational internal estimates

Looking at growth rates there is evidence, however, that costs in Europe are rising faster than they are in the US (see Figure 40).

Figure 40: Increase in cost per patient growth by country: 1991-2000 (nine-year CAGR %)



Source: Fasttrack systems

Looking at the index of complexity for trials undertaken in Europe compared to the US, we find they are equal using a measure of the average number of procedures per patient. However, when we compare the mean cost per patient we find the cost in Europe is 52% of those of the US.

Perhaps of most concern is the perception of Europe's performance regarding new technologies. Research commissioned by the European Commission finds "...the relative position of the US as a locus of innovation has increased over the past decade compared to Europe. Moreover, the overall picture suggests that Europe's performance is comparatively worse in biotechnology."⁶³ In Europe, the pharmaceutical industry has not effectively applied new technology to become specialists in particular areas, which US firms have done.

7.3 Financing R&D

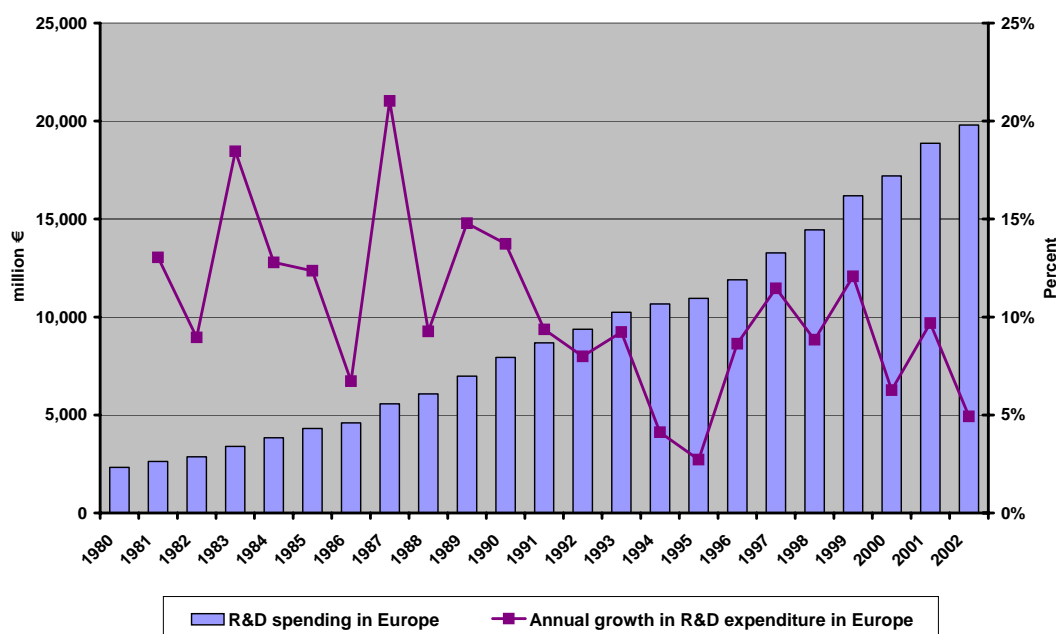
Finally, it is possible that the cost of financing R&D expenditure rose increasing the costs of developing new products. In a recent study on innovation in the pharmaceutical industry, the FDA has identified the investment climate in the 1990s as one possible factor contributing to the decline in new product applications seen in the US.

⁶³ Gambardella, Orsenigo, and Pammolli (2000).

“With total development time averaging about ten years, today's applications are the result of R&D that began a decade ago. Industry data show that in the early nineties, the growth rate in R&D investments dropped to the lowest level in 20 years. This dip may be having an impact now.”⁶⁴

In Figure 41 and Figure 42, the development of R&D expenditure in Europe and its annual growth rate since 1980 are presented both in nominal terms and adjusted for inflation. In nominal terms, R&D expenditure has increased continuously since 1980, but the drop in R&D growth identified by the FDA for the U.S. also occurred in Europe. In real terms, R&D spending dropped in 1981 and 1982 as well as between 1994 and 1996 compared to the previous years, as indicated by the negative growth rate in these years.

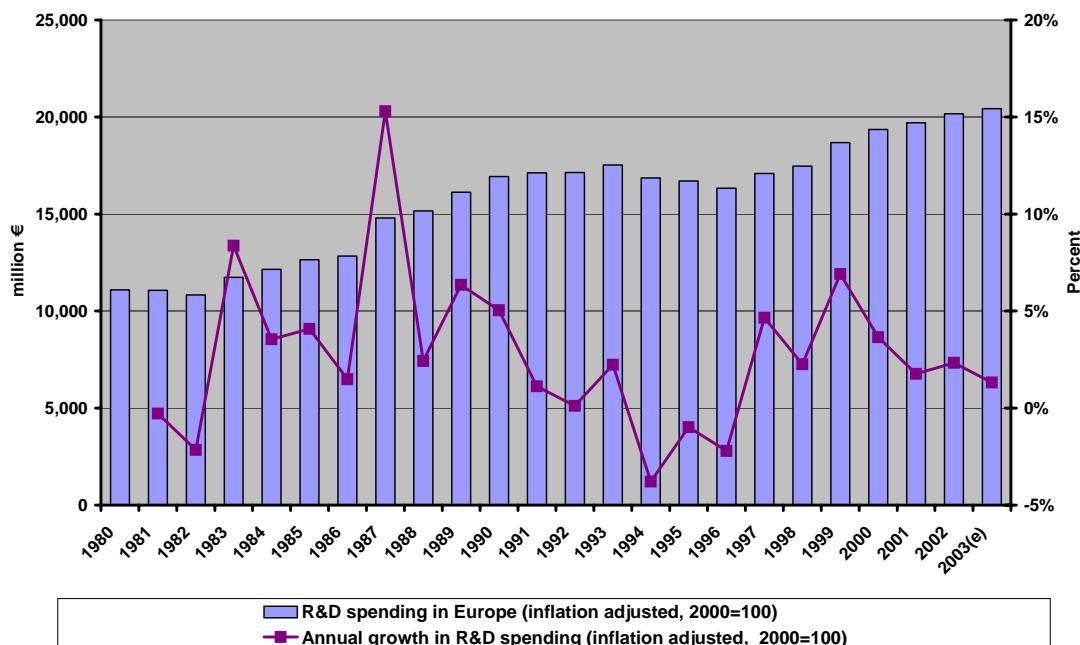
Figure 41: Level and annual growth of R&D spending in Europe in nominal terms



Source: EFPIA member associations and CRA calculations.

⁶⁴ FDA (2003).

Figure 42: Level and annual growth of R&D spending in Europe in real terms (inflation adjusted)



Source: EFPIA member associations and CRA calculations. Inflation rate taken from Datastream.

Both graphs indicate an external shock to R&D expenditure growth in the mid-1990s. Between 1980 and 1989, growth of R&D spending was highly volatile, but – at least in nominal terms – relatively stable. In 1990, a period of drastic decline in the growth rate began, both in nominal and real terms. The most significant fall occurred in 1994, when the growth rate plummeted by 50%, from close to 10% to about 5% in nominal terms and from 2% to –4% in real terms. In nominal terms, the turning point of the dramatic decline was reached in 1996, when the growth rate jumped back up, close to its 1993 level of around 10%. In real terms, growth became positive again in 1997. Still, the general downward trend seems to have continued and in 2002, the growth rate of nominal R&D expenditure in Europe was only 5%, a quarter of its value in 1987. In real terms, growth of R&D expenditure in Europe was 2% in 2000, only 13% of its value in 1987.

Considering external measures of investor confidence in the pharmaceutical sector we do not find any evidence to relate a loss of investor confidence to the drop in R&D investment in the early 1990s. It seems that pharmaceutical stock prices, a possible proxy for investor confidence in the sector, closely followed the overall stock price development and there is no “pharma effect” discernible.

7.3.1 THE ROLE OF VENTURE CAPITAL

During the CRA roundtable with industry experts and regulators, it was highlighted that especially for small pharmaceutical companies in the biotechnology industry, access to capital is crucial. For big pharmaceutical companies, funding is generally not a problem and, as a consequence, many small pharma companies have teamed up with larger firms in order to benefit from the capital base of the latter. Venture capital represents an alternative solution to the problem of sufficient funding for smaller firms. However, in Europe access to venture capital is said to be especially difficult due to three main reasons:

- Venture capital firms are usually interested in returns within two to three years, which is not the appropriate time horizon for the development of pharmaceutical products;
- In the US, public funding from the National Institute of Health (NIH) effectively complements venture capital funding; and
- Owners of small pharmaceutical companies in Europe are reluctant to hand over control over their company to venture capitalists.⁶⁵

7.4 Summary

Although it is possible to argue over the particular methodology used, there is considerable evidence to show that cost of researching and developing a new pharmaceutical product has increased. Over the last decade there has been a five-fold increase in the costs of clinical development, compared to a 60% increase in the real costs of preclinical development.⁶⁶

These costs have been rising even though it appears that pharmaceutical companies have been more effective at stopping investment on products that are not going to make it to market and have reduced overall time between synthesis and launching the product.

In this section we have reviewed some of the reasons why costs may have risen so dramatically:

- There is clear evidence that the cost of research and development varies by therapeutic group and that the mean cost of undertaking clinical trials rises with the complexity of the product. However, it is less clear that the product areas that have seen the most significant growth over the last five years or where future growth is predicted are systematically more complex than those focused on in the past. Therefore, although this is likely to contribute to the rising costs, we see this as only part of the explanation.
- There is however some evidence that the number of trials required to support a new product has risen over the last ten years. This is thought to be due to a number of factors. In particular, the need to have comparative studies to support marketing,

⁶⁵ CRA roundtable on 26 June 2004.

⁶⁶ DiMasi, Hansen, and Grabowski (2003).

formulary negotiations and reimbursement decisions has increased the number of head to head trials.

- There is no compelling evidence that regulatory requirements have been a major component in the long-term increase in costs. They may however have led to an increase in costs in the late 1990s, due to a number of marketing authorisation withdrawals. There may be offsetting effects due to increased standardisation on the one hand but greater compliance costs regarding patients on the other hand.
- Regarding new technology there is a general consensus that this has increased the costs of research and development in the short-term. There is less consensus regarding how quickly these costs will pay back and whether this will result in the cost of development falling back to the original level or lowering costs dramatically.

We have also reviewed the implications of the changing costs of research and development for innovation within the EU. This is potentially alarming as there appear to be two significant threats:

- A cost based threat based on the lower research and development costs from lower income parts of the world.
- A loss of competitiveness to the US even though there appears to be a cost advantage in undertaking trials in Europe.

8 Phase II: The returns to research and development

Firms undertake investment in research and development in the expectation of future profits. Changes in the regulatory and reimbursement system can affect the returns to innovation, and thereby the incentives of pharmaceutical companies to invest in R&D, in a number of ways. In this section we investigate how the following changes in regulatory and reimbursement structure impact on the incentives to innovate:

- Tougher price regulation;
- Increased competition from generics;
- Therapeutic reference pricing;
- Changes to the effective data protection and market exclusivity period;
- Risk sharing between payers and pharmaceutical companies; and
- Measures to ensure cost-effectiveness.

8.1 Price regulation and parallel imports

We would expect the amount that pharmaceutical companies invest in R&D to be related to the overall returns to innovation. If the returns to innovation were to rise we would expect to see greater amounts invested in the future. This intuitive reasoning has been confirmed by several empirical studies. Troyer and Krasnikov (2002) found that limiting sales growth in pharmaceuticals through price control negatively influences innovation. The authors analysed the effect of Medicaid rebates for medicinal products on innovation in the US pharmaceutical industry.⁶⁷ Their results show that the Medicaid rebates are likely to reduce the number of new drug applications filed per year with the FDA by 1.24 and the annual number of new drug applications approved by the FDA by 4.13. Hence, the opportunity costs of the Medicaid rebates in the US are more than 4 newly approved drugs per year.⁶⁸ In

⁶⁷ The US Medicaid programme was established in 1990 and includes two key rebate provisions, namely a most-favoured-customer clause for prices of drugs supplied to Medicaid recipients and a discount of at least 15.1 percent on the wholesale price of branded medicinal products (Troyer and Krasnikov (2002), p. 88).

⁶⁸ Troyer and Krasnikov (2002), pp. 87-96. Using data for the time period 1970 until 2000, the authors analyse the relationship between US pharmaceutical industry revenues and industry innovation as measured by the “number of approved NCEs”, the “number of new drug applications approved”, the “number of new drug applications filed” and the “number of commercial investigational new drug applications filed”. For all measures of innovation, the authors found a positive joint effect of the sales growth variables on innovation, but the coefficients are only statistically significant (at the five percent level) for “new drug applications approved” and for “new drug applications filed”. Based on the results of their model, the authors conclude that limiting sales growth through rebates or other price regulation will negatively affect growth of industry innovation. Assuming that the entire amount of the Medicaid rebates would have been added back to sales, the authors predict that due to higher average annual growth in sales, the number of new drug applications

another study, the US Health and Human Services Department found in 1994 that in Germany, Sweden, the United Kingdom and France, government spending control with regard to medicinal products resulted in lower R&D spending by companies. In particular, a decrease in drug prices by 1 percent was found to lead to a fall in R&D spending of 0.68 percent.⁶⁹

Given that prices of newly launched, innovative medicinal products are regulated in almost all European countries, profits of pharmaceutical companies crucially depend on national price regulation and reimbursement systems.⁷⁰ In the recent past, we have seen increasing cost containment measures being introduced across all EU Member States. To the extent that these measure reduced prices or the reimbursement of medicinal products, they can be expected to also reduce the returns to innovation and thereby the incentives for companies to invest in R&D.

Examples of recent cost containment measures that reduced prices and consequently returns to innovation include the following:

- In Denmark, there has been a succession of price freezes since the beginning of 1994. The latest, in 1998, meant that prices of prescription and reimbursable OTC drugs were frozen until March 2000.⁷¹
- In Germany, a mandatory discount on patented products was recently introduced. Since 1 January 2003, the “Beitragssatzsicherungsgesetz” (law to secure contribution rates) obliges manufacturers to grant a discount on the retail prices of their products when these are sold to members of the statutory sick funds.⁷² Initially the discount was set at 6 percent and has been increased to 16 percent for 2004.⁷³
- In Spain, where pharmaceutical prices are set by the Ministry of Public Health and Consumer Affairs through negotiations with the pharmaceutical industry, negotiations have at times resulted in profit-payback agreements and/or price reductions. For instance, a 6 percent price reduction was applied to all pharmaceutical products over a certain price in 1999.⁷⁴

approved would have been higher by 4.13 and that the number of new drug applications filed would have been higher by 1.24 per year respectively from 1992 until 2000.

⁶⁹ US Department of Health and Human Services (1994), discussed in Troyer and Krasnikov (2002), p. 88.

⁷⁰ To our knowledge, there are currently only two EU Member States – Germany and the UK – that do not directly control the pricing of innovative, patented pharmaceuticals. However, pricing freedom in the UK is limited by the Pharmaceutical Price Regulatory Scheme (PPRS), which allows free pricing as long as a company’s UK profit is less than the allowable return on capital employed (ROCE). In Germany, reference prices will be set for some patented products in the course of 2004. See e.g. Kanavos (2002), pp. 2-10; and Wallerstein (2004).

⁷¹ Macarthur, Donald (2000), p. 23.

⁷² German government press release of 1 January 2003.

⁷³ Press release of the German Ministry for Health and Social Security, 12 April 2004. Note that the increase of the discount to 16 percent was implemented in anticipation of new reference prices for patented products which are expected in the course of 2004 (before 2004 only off-patent medicines could be assigned a reference price in Germany). For products with a reference price, manufacturers will not have to grant the discount.

⁷⁴ Macarthur, Donald (2000), p. 98.

- In the UK, the Pharmaceutical Price Regulatory Scheme (PPRS) imposed a 4.5 percent price cut through modulation in 1999. The current PPRS ends in September 2004. It is unclear what implications this will have for the price of branded products. This is still being negotiated as we write.

In addition to regulatory price control, other measures can reduce the overall returns that pharmaceutical companies generate with innovative products. For example, revenues of brand manufacturers from an innovative prescription drug can be eroded by parallel imports. Some high-price countries, e.g. Germany, the Netherlands and the UK, promote the use of parallel imported pharmaceuticals, usually by providing incentives to or levying obligations on pharmacists to dispense products imported from low-price countries such as Spain and Greece.⁷⁵ In Germany for example, the health reform law passed in September 2003 re-introduced a requirement for pharmacists to dispense an imported drug for a prescribed medicine if parallel imports are at least 15 percent or €15 cheaper.⁷⁶

In the recent review of the EU pharmaceutical legislation a provision has been added saying that all members of the distribution chain of a medicinal product in a given country, i.e. marketing authorisation holders as well as distributors and importers, are individually responsible (within the limits of their responsibilities) for ensuring appropriate and continued supplies of the product so that the needs of patients in the concerned Member States are covered.⁷⁷ Some industry experts have argued that this provision might make it more difficult for manufacturers to impose restrictions on distributors as a way of limiting parallel imports of their products to more expensive markets.⁷⁸ However, the European Commission's intention was to ensure the availability of medicinal products in all Member States and to avoid situations where supply in one Member State is too low because products have been exported to other, more expensive markets by parallel traders.

8.2 Generics

In most European countries we are seeing efforts to encourage greater generic competition after the patent of an innovative product expires. Strong generic competition usually leads to

⁷⁵ Kanavos (2002), pp. 26-27.

⁷⁶ Draft law for the modernisation of the German statutory sickness insurance of 8 September 2003, p. 75. Already before the health reform, pharmacists had an obligation to dispense imported medicines in certain cases. Until April 2002, pharmacists had to substitute imported medicines if they were at least 10 percent cheaper than domestic drugs (Verband Forschender Arzneimittelhersteller (2003)). In April 2002, the minimum price differential requirement was abolished. Instead, sick funds and pharmacists had agreed that imported drugs should account for a specific share of pharmacists' total revenue (5.5 percent in 2002 and 7 percent in 2003, see Rahmenvertrag über die Arzneimittelversorgung (2001), para. 4.

⁷⁷ European Commission (2001), Article 81. See also *Scrip*, 10 March 2004.

⁷⁸ *Scrip*, 10 March 2004. One example of a manufacturer trying to limit parallel trade was the Adalat case in which Bayer restricted supplies to wholesalers exporting from Spain and France. At the time, the European Court of First Instance found this move to be legal (Kanavos (2002), p. 27).

rapid volume and price erosion for the original, branded product after patent expiry. Meaning that more of the returns to an innovative product occur in the pre-patent expiry period.

Traditionally generics have been at a low level in many countries, e.g. in France and Spain they accounted for only eight and three percent of total medicines sales in 2001.⁷⁹ In countries such as the UK and Germany, generics have been significant for many years. In 1999, generics accounted for 16% of drug retail sector value in Germany and for 15% in the UK.⁸⁰ In the UK, most GP prescriptions are written by generic name, leading to the largest generic sector in the EU. In Germany, the *aut idem* rule, in effect since July 2002, obliges pharmacists to dispense a generic if the branded product is priced above a certain threshold.⁸¹

In the last few years, even countries that have not traditionally encouraged generics have adopted policies to promote generic competition:

- In Belgium, prices for generics have always been significantly lower than for innovator brands.⁸² This difference has become even more pronounced since changes in 2001 have led to a situation in which only generics that are priced at least 26 percent below the branded product are reimbursed by the sick funds. This has resulted in a significant reduction in revenues post patent expiry as we are seeing significant price erosion due to generics for the first time. In addition, there is also a mandatory price reduction of 12 percent for products that have been reimbursed for longer than 15 years, reducing returns post patent expiry even further.⁸³
- In France, generic erosion has traditionally been minimal because the local generics industry was underdeveloped compared to other European countries. In 2001, only eight percent of total unit sales in France were generic products.⁸⁴ Recent policy changes are now expected to encourage earlier entry and more rapid price and volume erosion following generic entry. In 1999, pharmacists were given the authority to substitute generic products for the prescribed brand as long as the physician does not explicitly forbid substitution.⁸⁵ In addition, beginning in 2000, generic manufacturers were able to submit for marketing authorization prior to patent expiry, allowing them to launch immediately upon patent expiration.⁸⁶ Most recently, in July 2003, a reference pricing system was introduced under which all products in a generic reference group are reimbursed at a single reference price. Patients must pay the difference between the brand price and the reference price. It is expected that branded manufacturers will respond to this by reducing prices to the reference price level.⁸⁷
- In Spain, the government implemented reference pricing in December 2000, under which reimbursement would be limited to the generic price for products subject to

⁷⁹ PPR Communications Ltd (2002), pp. 55 and 127.

⁸⁰ IMS Health (2000).

⁸¹ The physician may explicitly exclude the possibility of generic substitution on the prescription.

⁸² Macarthur (2000), pp. 12-20.

⁸³ PPR Communications Ltd (2002), p. 25.

⁸⁴ PPR Communications Ltd (2002), p. 55.

⁸⁵ Macarthur (2000), p. 41.

⁸⁶ Macarthur (2000), p. 41.

⁸⁷ *Scrip*, 12 March 2003, p. 2.

generic competition. This action, combined with other policy initiatives designed to encourage the use of generics, led to a significant increase in generic penetration for 2002 and expectations that generic use will continue to increase.

- The recent review of the EU pharmaceutical legislation generally encourages generic competition, e.g. by ensuring that generic manufacturers can only enter the market 10 years after the reference product, but are allowed to start development work in the EU eight years after the reference product was put on the market, i.e. two years before market exclusivity and potentially even the patent of the branded original product expire (the so-called “Bolar” provision). Also, market access for generics is planned to be facilitated, e.g. by reducing the administrative burden for generics with regard to the documentation necessary when applying for a marketing authorisation.⁸⁸

The impact of increased generic competition and resulting erosion for branded originals could affect the incentives to innovate in a number of ways:

- Increase the importance of the branded period and reduce the expected time until a product is lost as a revenue generator, hence provide incentives to channel resources into R&D for new products that will gain acceptance quickly in order to keep a competitive product portfolio;
- Increase the incentive to focus on incremental innovations that will lead to a further period of market exclusion such as slow release formulations or new indications.

If pharmaceutical companies face strong generic competition, the branded period will be of primary importance for their revenue and profit streams. Assuming that firms need a portfolio of several successful and revenue and profit generating products in order to remain competitive and diversify risk, strong generics reduce the expected lifetime of each of the products in the firms’ portfolios and will therefore provide an incentive to channel investments into R&D for new products that will get through the authorisation procedure and will be adapted by the market more quickly so that the firm will be able to keep its portfolio “complete”.

Bringing completely new products to the market is only one possible way for companies to maintain a competitive product portfolio. Another, and less risky, option is for manufacturers to prolong the lifetime of successful products by extending the patent period. Obviously it is not possible to get a new patent for an old product, but firms can focus on incremental innovations, e.g. controlled-release formulations of a substance. Assuming that a large share of prescribers and patients would adapt to the incrementally modified and enhanced version of the original branded product instead of switching to generic versions of the basic substance, incremental innovations can protect a brand from too high a level of generic erosion and thereby ensure a continued revenue stream and stable product portfolio. However, while being profitable for the individual companies, the channelling of resources into R&D on incremental innovations instead of really new products might not be the most

⁸⁸ *Scrip*, 10 March 2004; and European Commission (2001), pp. 5-6.

efficient resource allocation from a social point of view. A more worrying concern is that the pressure of generics can lead to companies holding back on innovation, such as new formulations, until near patent expiry, when incremental innovation is required to protect revenues. This incentive to delay innovation will reduce social welfare.

8.3 Therapeutic reference pricing

Competition in the pharmaceutical market is often characterised as “virtuous rent seeking” with competitors competing for a market rather than in the market, i.e. pharmaceutical companies compete through investing in research and development. The company who succeeds in getting a patent and bringing the product to the market first wins the “game” (i.e. initially the total market) and makes the greatest return. However, this view is an oversimplification. Me-too products, i.e. products with a similar but different molecule that are in the same therapeutic area, usually compete with the innovator product.

The way me-too and innovator brands compete has important effects on the incentives to innovate and is likely to change as therapeutic category reference prices for patent-protected drugs develop in the EU Member States. Traditionally, reference prices have been used at substance level, i.e. for generics. If reference prices were set for patented drugs, this was typically to determine their maximum retail price or reimbursement level in the given country, usually in relation to prices for the same product in other countries. One example is the Netherlands, where the maximum price for a product will be set on the basis of the average price of comparable pharmaceuticals (based on active substance) on accepted product lists in Belgium, Germany, France, and the UK.⁸⁹ So far, the Netherlands is the only EU country using therapeutic reference pricing. Italy has introduced a reference price system for patent-protected products, based on a classification of products into homogeneous groups that are defined as “substances whose safety and efficacy profile is substantially overlapping in the practice of family medicine”. The ATC code is used as a starting point, but if necessary classification is adjusted in accordance with this definition. For each class, a reference price is determined which represents the maximum level of reimbursement. Products that are more expensive than the reference price are not reimbursed at all, i.e. there is no system of co-payment.⁹⁰

As of 1 January 2004, Germany has re-introduced reference pricing for patented substances that are pharmacologically and therapeutically similar. In December 2003, suggestions were made for five new reference price substance groups that should be assigned a common reimbursement level, but a final decision is only expected for mid-2004. “Therapeutic

⁸⁹ Macarthur (2000), pp. 79-80.

⁹⁰ Reimbursement is limited to the average daily dose cost of the active substance that has cumulative 60 percent market share in the defined daily dose (DDD) and cumulative 50 percent market share in value (for classes in which no active ingredient has more than 50 percent market share) or to 15 percent above the average daily cost of the active ingredient in the class that has a market share of at least 5 percent (see Wallerstein (2004).

innovations” are excluded from the reference price system, but a working group is still discussing the proper definition of such an innovation.⁹¹ Pharmaceutical companies active in R&D have claimed that the new system will not affect their pricing decision and that they will keep their prices at current levels. This has caused some public concern since it would mean that instead of leading to lower prices, the new system could lead to significantly higher co-payments for patients.⁹²

Reference price systems for patented products, like the ones described in Italy and Germany, change the basis of competition between innovator brands and me-too products significantly. Historically, the first entrant is able to charge a price premium. The second entrant faces a harder bargaining position, as he usually needs to offer a discount compared to the innovator brand to justify reimbursement.⁹³ Given that the innovator brand is already on the market, the me-too producer has a significantly weaker bargaining position as delaying the introduction of a me-too may not have the same implications as delaying the innovator brand (in terms of leaving an unmet need). This weaker position often results in the innovator brand being able to justify and maintain a higher price than the me-too brands.

With therapeutic reference pricing, the market entry of a second, similar product that will be grouped with the innovator brand in a new reference price class directly reduces the price of the latter brand. This reduces the incentives of being first in an area where there are likely to be me-too competitors. Hence, the prime effect of therapeutic reference pricing is a reduction in the returns to innovate and be the first in the market. On the other hand, it increases the incentives for product differentiation and to be as innovative as possible to position the own brand as unique with no me-toos likely to enter anytime soon. The incentive effect on innovation in me-too products will depend on the reference price set for a certain product category. If the category reference price is set above the price that me-too products could usually expect to achieve, the incentive to enter as a me-too competitor will increase compared to a situation without reference prices for patent-protected products. This would increase the incentive to invest in “copy R&D” instead of being truly innovative. On the other hand, if the category reference price is set below the usual me-too price level, the returns to me-too innovation will be reduced compared to a situation without reference pricing. Consequently, we would expect R&D spending on substances for which similar competitors are already in the market to decrease sharply. In the longer term, this could result in a lower

⁹¹ German Ministry for Health and Social Security (2004), pp. 2-3. Suggested product to be included in the reference price scheme are statins (annual sales to statutory sick funds of about €1.2 billion), proton pump inhibitors (annual sales to statutory sick funds of about €850 million), sartans (annual sales to statutory sick funds of about €670 million), triptans (annual sales to statutory sick funds of about €60 million) and certain anti-diabetics (annual sales to statutory sick funds of about €50 million).

⁹² Deutsches Ärzteblatt Online (2004).

⁹³ Note that this does not apply to Germany, where patented products have enjoyed pricing freedom until now and were all reimbursed by the statutory sick funds at their retail price level (taking the mandatory manufacturer discount of 6 and 16 percent into account in 2003 and 2004 respectively). The effect of reference pricing on returns to innovation described in this section would however apply to all EU Member States in which prices for reimbursed products are set through negotiations or other agreements (Austria, Belgium, Denmark, Finland, France, Greece, Ireland, Italy, Portugal, Spain and Sweden).

number of me-too products in the market and hence lower competition between them, possibly counteracting the desired price competition effect underlying the introduction of a reference price system in the first place.

Following the discussion above, it seems that the most important incentive effect of a reference price system for patented drugs on pharmaceutical innovation is a reduction in the returns to being first in the market. A secondary and more long-term effect is that it increases the incentive to invest in R&D of distinctive, differentiated products that are likely to remain without me-too competition for as long as possible. The question remains if this potential effect on the allocation of R&D spending, i.e. the focus on truly innovative new products instead of the improvement of already existing substances, will lead to the most efficient outcome from a social point of view. Troyer and Krasnikov (2002) point out that the competitive case might actually lead to too much innovation from a social welfare perspective.⁹⁴ Hence, focusing R&D activities on truly innovative and differentiated products, although possibly leading to a fall in the number of new marketing authorisation applications and approvals, could also be welfare enhancing. Yet, an evaluation of the dynamic welfare effects of innovation are beyond the scope of this study and could be the focus of future research.

8.4 Data protection and market exclusivity period

Extending the length of the data protection and market exclusivity period or granting variable protection and exclusivity periods depending on the type of medicinal product will increase the returns on innovation that pharmaceutical companies can expect to realise. Hence, the incentive to invest in R&D should increase too.

The recent review of the European Union's pharmaceutical legislation has led to the harmonisation of the data protection and market exclusivity period for products authorised in the European Union. According to the new Directive, authorisation holders can receive an extra year of market exclusivity if they identify a significant new indication for their drug.⁹⁵ This provision should increase the incentive for pharmaceutical companies active in R&D to invest in further research into and improvements of their already marketed products. However, it is important to note that the new EU legislation for pharmaceuticals has also introduced the "Bolar" provision according to which producers of generics can start their studies and clinical trials prior to patent expiry of the reference products. Clearly, this reduces the "protected" time period for producers of branded products by allowing generics to enter the market immediately after patent expiry instead of starting studies and trials only then.

By offering additional market protection for specific types of products, the authorities can influence the allocation of R&D expenditure and support areas of innovation that might be

⁹⁴ Troyer and Krasnikov (2002), p. 95.

⁹⁵ See e.g. *Scrip*, 10 March 2004.

desirable from a social point of view, but do not offer sufficient expected returns to attract the R&D interest of companies in the absence of additional support measures. EU wide examples of such areas in which returns on innovation have been or are planned to be changed in the future through regulatory provisions are orphan drugs and medicinal products used in paediatric patients.⁹⁶ In this section, it should suffice to say that for investment in both orphan and paediatric drugs, pharmaceutical companies are rewarded by extended market and data protection periods, thereby increasing the returns to innovation and the incentive to invest in these areas.

8.5 Risk sharing between payers and pharmaceutical companies

In a number of countries, providers and purchasers share some of the risks associated with bringing innovative products to the market. Particular examples of this include:

- The provider commits to a level of volume and a price level. If the volume should be higher than this, there will be a corresponding discount on the product. One example is France, where the reimbursement price is set through negotiations between the drug's supplier and the authorities. The system provides for a payback clause if the budget agreed upon in the negotiations is exceeded. In Italy, there is the possibility of payback clauses, possible price reductions or delisting of products if sales rise above the levels agreed during price negotiations.⁹⁷
- The provider commits to a particular outcome, for example in the UK, the high price and reimbursement of products for some diseases is conditional on their long-term effectiveness. This has allowed the product to be reimbursed while leaving the risk regarding its effectiveness with the providers. It is generally accepted that this is only likely to be appropriate for products where their effectiveness can only be assessed over the very long-term.

Mechanisms such as this change the pay-offs from innovation. To some extent they reduce the risks to providers of getting products reimbursed, however, they may also significantly increase the risk of a product proving ineffective in the longer term or place a cap on the usage of the product. Indeed, the most extreme example of this is profit capping as seen in the UK, where if profits rise above a given level, it will be necessary for the provider to lower price and rebate to the Government. Although, in principle, the impact of risk sharing could be to raise or lower the incentive to innovate, in the current climate of cost containment, these mechanisms are often asymmetric. That is, they limit the upside from a successful product without necessarily insuring the provider against a product that does not prove to be as

⁹⁶ For a detailed description of the European Commission's planned paediatric medicines regime see e.g. European Commission (2004).

⁹⁷ Kanavos (2002), pp. 8-9.

effective as originally thought. In this case, they are likely to dampen the incentive to innovate.

8.6 Measures to ensure cost effectiveness

In general, cost containment measures of one sort or another have been used in all European Union countries. Pharmaco-economic studies on a drug's cost effectiveness are an increasingly popular policy that is specifically targeted at innovative medicines, which are often priced at a premium compared to other drugs.⁹⁸

*Traditionally, pharmaceutical companies were required to provide evidence to demonstrate their product's safety, efficacy and quality for purposes of registration and reimbursement. Increasingly, a fourth hurdle has been added which requires that companies demonstrate the economic value of a product to be reimbursed.*⁹⁹

So far, pharmaco-economic analyses have not been used in the EU as criteria in the marketing authorisation process for new medicinal products. The desire to improve information on cost effectiveness is illustrated by EURO-MED-STAT an ongoing project funded by the Directorate General for Health and Consumer Protection of the European Commission and co-funded by the National Research Council of Italy.¹⁰⁰ EURO-MED-STAT aims at developing indicators for monitoring price, expenditure and utilisation of medicines in Europe and to build a European database of licensed medicines to that effect. Apart from providing more up-to-date information than the EURO-Medicines Database the Euro-Med-Stat Database would also provide information on prices (per pack, per DDD) and allow more complex searches that would allow the user to compare the availability of medicines, active ingredients, or trade names between countries. The data is not yet publicly available.

Today, pharmaco-economic analysis is being used in Denmark, Finland, Ireland, the Netherlands, Portugal, Sweden and the UK, either in the course of determining a new product's reimbursement price or for use in prescribing decisions. France and Italy use cost effectiveness analyses too, although in a less formalised way.¹⁰¹

The French system links therapeutic improvement to both the product price and the maximum reimbursement level. For each medicinal product applying for inclusion in the list of reimbursable medicines in France, the Transparency Commission (Commission de la Transparence) prepares an opinion, including an assessment of medicinal, pharmaceutical, epidemiological and economical aspects of the product. In 1999, the evaluation system was fundamentally changed by a decree fixing the criteria of the medicinal service delivered

⁹⁸ Kanavos, Trueman and Bosilevac (2000), p. 32

⁹⁹ Mullins, Ndiritu, Yoder and Shaya (2003).

¹⁰⁰ <http://www.euromedstat.cnr.it/default.asp>

¹⁰¹ Dodds-Smith and Bagley (2003).

(service médical rendu, SMR) which serves as the basis for determining the reimbursement of a specific product. Products that are found to provide an “important” SMR will be reimbursed at 100 percent, while products with a moderate or low SMR will be reimbursed at only 35 percent of their price. The majority of products, which does not fall in either of these two categories, is reimbursed at 65 percent of their price.¹⁰²

In its work, the Commission de la Transparence also assesses the improvement in SMR of a specific product compared to other products available in the market for the same indication (amélioration du service médical rendu, ASMR). There are five possible levels of ASMR:

- I. Major therapeutic progress (breakthrough)
- II. Important improvement in terms of therapeutic effectiveness and/or the reduction of undesired side effects
- III. Moderate improvement in terms of therapeutic effectiveness and/or the reduction of undesired side effects
- IV. Minor improvement in terms of acceptability, convenience to use and compliance
- V. No therapeutic improvement, but the product should be reimbursed
- VI. No therapeutic improvement and the product should not be reimbursed¹⁰³

Overall, the French system clearly rewards therapeutic improvements and provides an incentive for firms to invest in breakthrough or at least important pharmaceutical innovations.¹⁰⁴

In the UK, the National Institute for Clinical Excellence (NICE) was established in 1999 with the task of assessing the clinical and cost effectiveness of newly authorised medicinal products. These appraisals lead to prescription recommendations, which are aimed at helping “health professionals in the [National Health Service] give patients the best possible health care within the resources available.”¹⁰⁵ In its assessment, NICE considers three main criteria: the product’s clinical effectiveness, its cost effectiveness and the wider NHS implications of the product’s availability. While – according to the UK government – NICE recommendations do not limit the exercise of case-by-case clinical judgment on the part of

¹⁰² Agence française de sécurité sanitaire des produits de santé (Afssaps) (2002), p. 95, Commission de la Transparence (2004), and Wallerstein (2004).

¹⁰³ General information on Afssap at <http://agmed.sante.gouv.fr/htm/5/avisct/indact.htm>; Afssaps (2002), p. 95, Commission de la Transparence (2004), and Wallerstein (2004).

¹⁰⁴ For products with an ASMR level of I or II, the price will be set “in coherence” with other EU G5 prices. For an ASMR III, prices are set at the same level if total reimbursed retail sales of the product are forecast to be below €40 million. For products with forecast reimbursed retail sales of €40 million or more, prices are negotiated between producer and regulator and the producer can usually expect the same price level as competitor products, sometimes even a small price premium. For products that are found to have an ASMR of level IV, prices are negotiated and producers can expect a small discount on prices of competitors that are already in the market. Products with an ASMR of V will only be eligible for reimbursement if they are priced at a 30 percent discount compared to already marketed products, i.e. if they result in net economic benefits. Wallerstein (2004).

¹⁰⁵ NICE (2004).

prescribers, health authorities usually follow them in their reimbursement decisions. A product that does not obtain a positive NICE judgment is often not stocked in hospital pharmacies and prescription is de facto very difficult. However, contrary to the French system, NICE does not explicitly affect the price of a given product.¹⁰⁶

There is no statutory obligation for pharmaceutical companies to provide data to NICE, but most companies are keen to be involved in the appraisal procedure. Still, the problem of data availability for clinical and cost effectiveness assessments has been one of the main criticisms brought against NICE's work. The data necessary for an assessment of the fourth hurdle, cost effectiveness, differ from the type of data companies are used to collect for the traditional three hurdles – efficacy, safety and quality – during the various phases of a product's development. Currently, most cost effectiveness assessments require some modelling on the part of both companies and authorities due to data limitations. In the future, cost effectiveness schemes might require companies to undertake not only safety and efficacy trials, but also “more pragmatic studies reflecting real world practice before submission to NICE or a similar agency.”¹⁰⁷ There are concerns that “the development of reliable cost-effectiveness data for pre-marketing approval and post-marketing re-appraisal will increase significantly the cost of developing all products”.¹⁰⁸ Increased R&D costs are likely to reduce the returns to innovation and thereby decrease the incentives for pharmaceutical companies to innovate.

In the UK, comments on the working of NICE have expressed concern that “they found the boundary between cost-effectiveness and affordability very blurred and that in practice NICE was being asked to undertake resource allocation.”¹⁰⁹ To the extent that cost effectiveness measures influence the allocation of health spending and ultimately R&D resources, there is a debate as to whether health authorities can determine the most efficient allocation from a social point of view. Kanavos et al. (2000) point out that a true social cost effectiveness analyses requires a full assessment of the social costs and benefits of a medicinal product “beyond those falling on the health service such as productivity losses brought about by a disease. However, when investing in treatments many health services diverge from a societal viewpoint to a payer perspective, whereby only those costs falling on the health service are considered.”¹¹⁰ This bias might lead to a stronger focus on cost containment than on medicinal innovation than would be beneficial from a social point of view, reducing the incentives to invest in R&D below the social optimum. Yet, Maynard and Bloor (2003) point to the fact that although the introduction of cost effectiveness studies has often been motivated by cost containment concerns, a true implementation of the fourth-hurdle

¹⁰⁶ Dodds-Smith and Bagley (2003), pp. 46-47. Note however that there have been reports of producers lowering the prices of their products in order to meet the cost-effectiveness threshold that NICE seems to follow implicitly, i.e. a value of £30,000 per Quality Adjusted Life Year (QALY, the cost effectiveness method used by the NICE).

¹⁰⁷ Kanavos, Trueman and Bosilevac (2000), p. 17.

¹⁰⁸ Dodds-Smith and Bagley (2003), p. 43.

¹⁰⁹ Dodds-Smith and Bagley (2003), pp. 48-49.

¹¹⁰ Kanavos, Trueman and Bosilevac (2000), p. 12.

mechanism will not necessarily reduce spending on pharmaceuticals. It may actually increase spending where cost-effective medicinal products are currently underused.¹¹¹ Hence, for some pharmaceutical companies cost effectiveness measures might actually increase the returns to innovation.

Cost effectiveness studies are likely to increase the R&D costs of companies who not only need to collect data on their products' efficacy, safety and quality, but also their pharmaco-economic value. Additional R&D costs will clearly reduce the incentive to invest in innovate products. On the other hand, irrespective of all potential pitfalls in their application to the real world that have been described above, pharmaco-economic analyses should increase the incentive for pharmaceutical companies to invest in the research and development of cost effective products that provide a true benefit to society instead of "wasting" resources on R&D for potentially profitable, but from a social perspective not very useful and effective drugs. In times of constrained health care budgets, cost effectiveness requirements might be the most efficient way to help allocate R&D resources efficiently.

8.6.1 CHANGING THE INCENTIVES REGARDING THE LOCATION OF R&D

In countries with profit restrictions due to cost containment measures (price cuts/freezes, reference prices etc.), total expected profits will be lower than in markets where pharmaceutical companies are able to set drug prices freely. The location of R&D activities can influence the ease of getting a product through the authorisation procedure and the success of later marketing activities (e.g. by establishing contacts with key opinion leaders in the respective countries which will positively affect prescribing once the product is on the market). Hence, one could expect that a pharmaceutical companies will invest a higher share of their total R&D spending in countries where quicker market entry and higher marketing success will generate higher profits and thus higher returns to innovation due to lower price restrictions. According to Gilbert and Rosenberg, "major R&D investments have recently followed clinical trials, which play a key role as a first step in successful commercialisation, to the US. It is appealing to companies to work with key US opinion leaders as they put together trials."¹¹²

However, this effect is likely to be blurred by other factors influencing the choice of R&D location such as the general climate for research, public incentives for general research, the location of experts, safety concerns etc. For example, Gilbert and Rosenberg mention the network effect among scientists, labs, universities and R&D suppliers, which contributes to the shift of R&D investments from Europe to the US.¹¹³

It may also be the case that implicitly or explicitly the negotiation with the payer is influenced by the level of R&D investment. For example, in the UK the Department of

¹¹¹ Maynard and Bloor (2003).

¹¹² Gilbert and Rosenberg (2004).

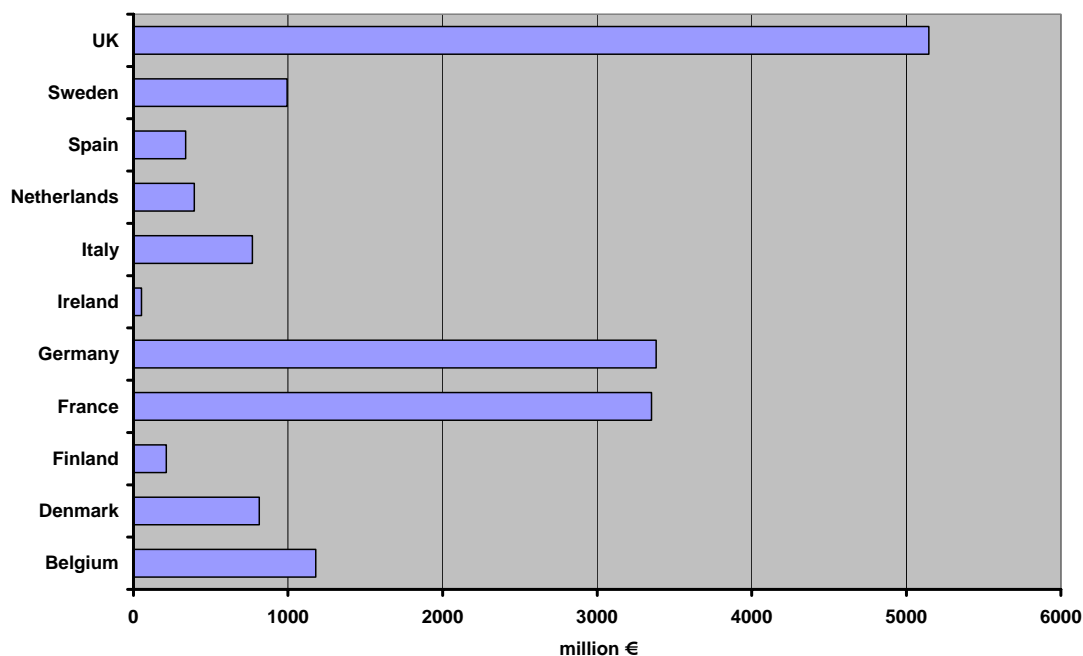
Health has a dual objective of getting the best price for the UK health system and developing the UK pharmaceutical industry. Indeed, under the PPRS there is an explicit incentive to have costs associated to the UK.

In addition, to the interaction with the reimbursement system, governments incentivise R&D by sponsoring blue skies research at universities directly. By allowing to share the costs of research programmes, this encouraged pharmaceutical companies to locate R&D in their countries.

In Europe, R&D spending was highest in the three major markets France, Germany and the UK in 2001 (see Figure 43). However, when put in relation to national market and production values (see Figure 44), the UK is the strongest R&D country in this group, with national R&D expenditure accounting for about 35% of national market sales (at ex-factory prices) and about 23% of national pharmaceutical production. In Germany, the share of R&D expenditure has traditionally been lower than in the UK. In 2001, it was only about 16% in relation to both market and production value. R&D expenditure in France in terms of market value is similar to the level in Germany and lower than in the UK. In 2001, R&D expenditure accounted for about 16% of market value. Interestingly, the share of R&D expenditure in relation to market value is very high in most of the Scandinavian countries, the home countries of AstraZeneca (Sweden) and Novo Nordisk (Denmark). R&D expenditure in relation to market value is also relatively high in Belgium, where GSK conducts a large part of its R&D activities.

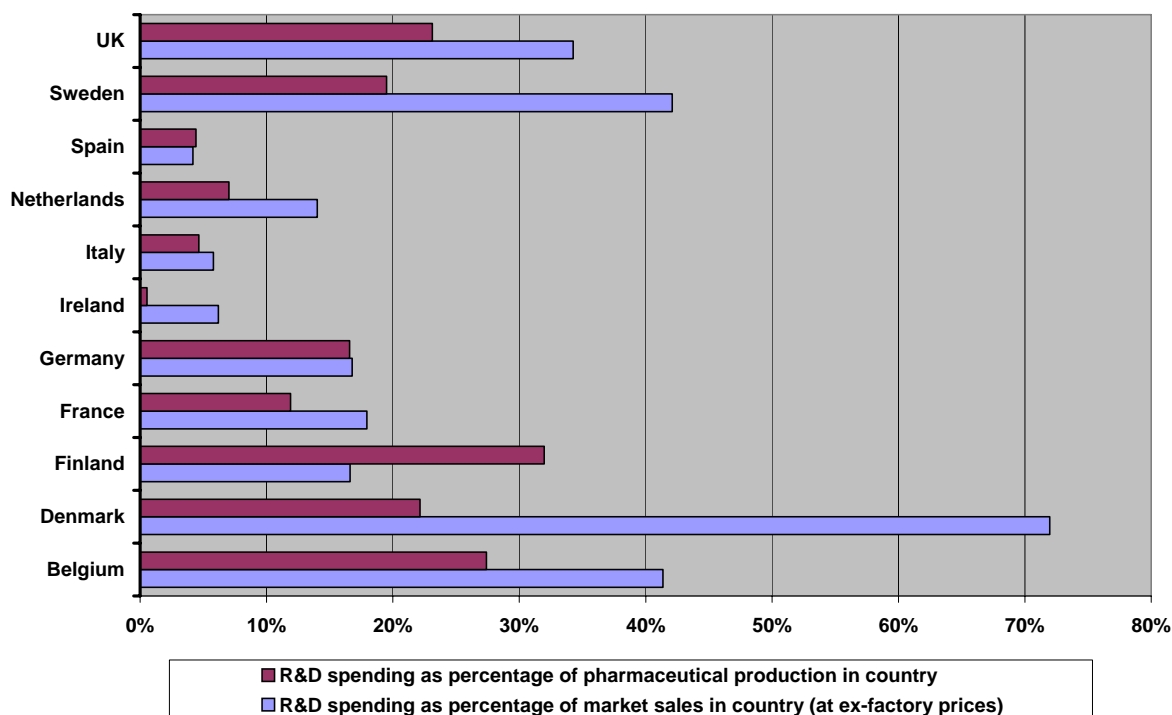
¹¹³ Gilbert and Rosenberg (2004).

Figure 43: R&D spending by country in 2001



Source: EFPIA (2003). Denmark, Netherlands: 2000 data. Belgium, Denmark, France, Ireland, Italy, Spain, Sweden: estimates.

Figure 44: R&D spending in relation to national market value and pharmaceutical production in 2001



Source: CRA calculations based on EFPIA data (EFPIA, 2003). Medicinal products as defined by Directive 65/65/EEC. National market value at ex-factory prices. Denmark: national pharmaceutical market value at pharmacy purchasing price. Austria, Belgium, France, Ireland, Spain, Sweden: national market values are estimates.

8.7 Empirical evidence on returns to innovation

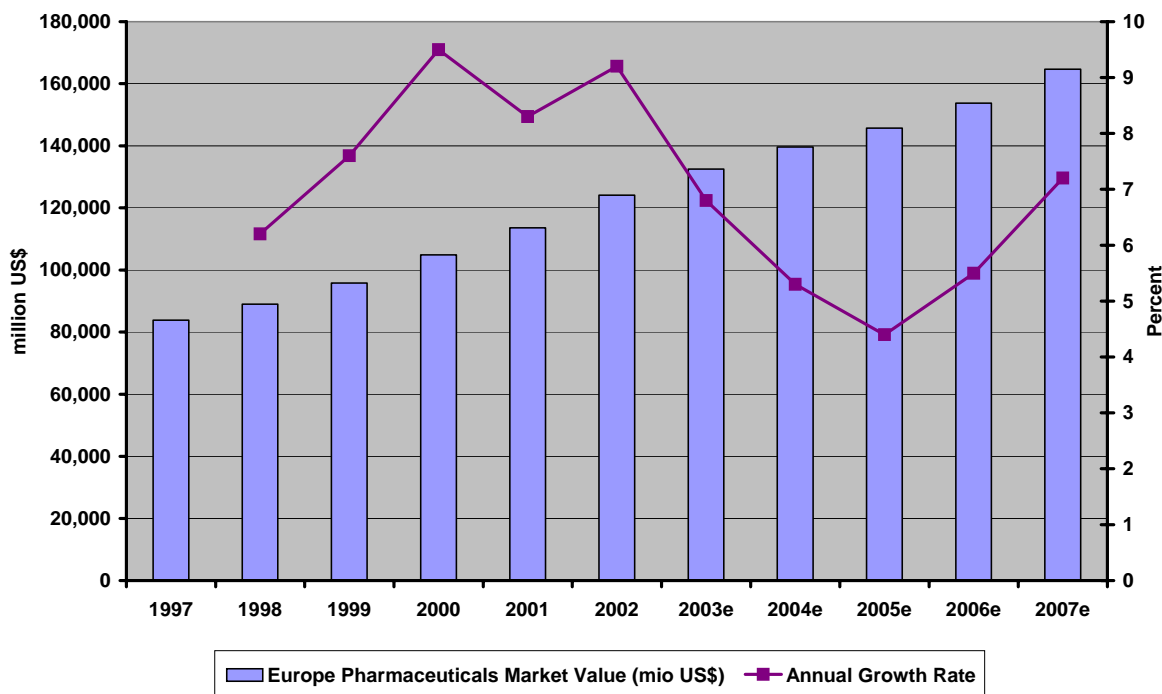
Almost all measures discussed above suggest that the expected level of future reimbursement has declined. However, in order to conclude on the effect on the returns to innovation it is necessary to take a number of further factors into account:

- Despite all the measures discussed above the spending on health care in general and pharmaceuticals in particular grows at a higher rate than GDP in most developed countries. According to the OECD, spending on pharmaceuticals accounted for 1.5 percent of the French GDP in 1992 and for 1.7 percent in 1998. In the UK, pharmaceutical spending increased from 0.8 percent of GDP in 1987 to 1 percent in 1992 and 1.1 percent in 1997.¹¹⁴
- Kanavos (2001 and 2002) points out that due to gross demographic factors and the general trend of population ageing in Europe, overall growth in demand for medicines is strong and higher than population growth. Indeed, Datamonitor (2003) found that “the fact that people require medicine regardless of the economic environment has enabled many large companies operating in this sector to maintain positive profit and revenue growth whilst companies in other industries have struggled” in the last few years due to the general economic slump and resulting falling investor confidence. Datamonitor expects the European pharmaceutical market to continue to grow until 2007, although at a slightly slower pace than in the period between 1997 and 2002. The compound annual growth rate of the European pharmaceutical market was 8.2% from 1997 until 2002 but is forecast to be only 5.8% between 2002 and 2007. Datamonitor attributes this to various market condition “challenges” that pharmaceutical companies face in Europe and that have been discussed extensively in this section, e.g. government imposed price cuts, the encouragement of generic competition, and price erosion due to parallel imports. Nevertheless, after declining growth between 2003 and 2005, Datamonitor predicts an increase in the growth rate in 2006 and 2007.¹¹⁵

¹¹⁴ Maynard and Bloor (2003).

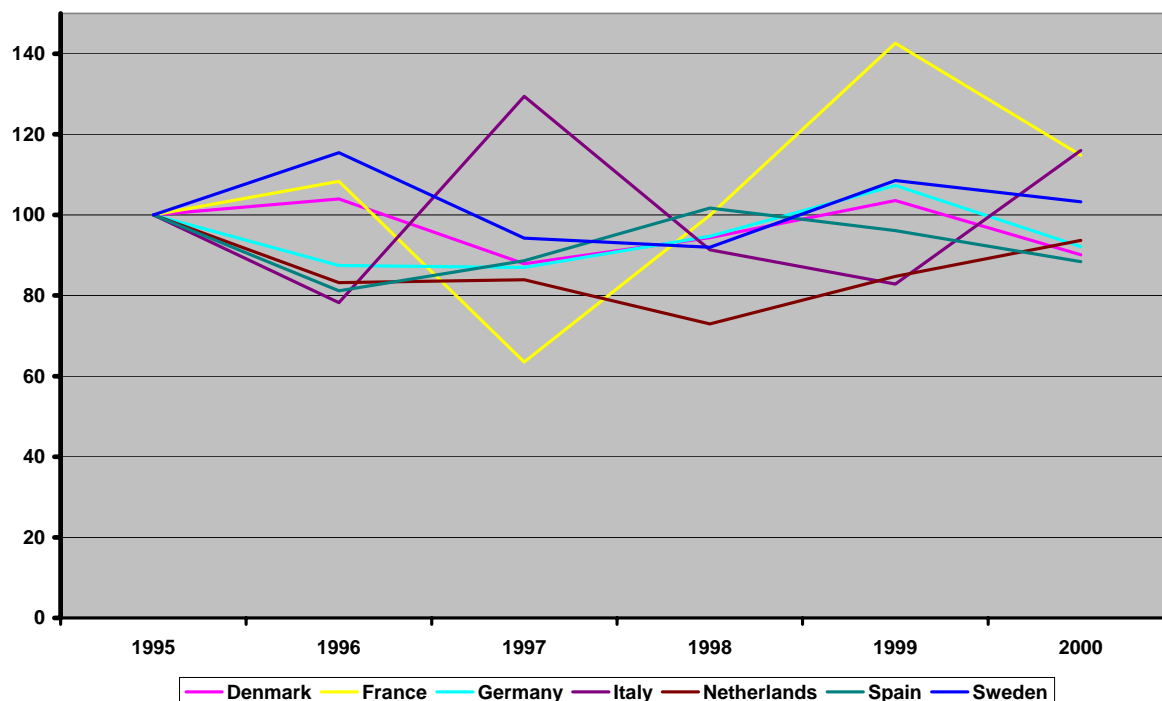
¹¹⁵ Datamonitor (2003).

Figure 45: European pharmaceuticals market value and annual growth rate (1997-2002 actual, 2003-2007 forecast, all in nominal terms)



Source: Datamonitor (2003).

- Kanavos (2001 and 2002) claims that despite general cost containment measures in Europe and despite the fact that medicine prices have not generally increased, the unit price of new medicinal products at launch is increasing in real terms. This statement is made in the context of a qualitative study of national reimbursement systems in Europe and was not confirmed by our quantitative analysis of prices of newly launched NCEs in a number of EU countries, as presented in Figure 46. Despite some volatility, there is no general upward trend in prices of new molecules in any of the European countries included in the analysis (the decision which countries to include was based on data availability).

Figure 46: Prices of newly launched NCE cohorts by year (1995=100)

Source: CRA calculations based on Department of Health and the Association of the British Pharmaceutical Industry (2002). The Department of Health and the Association of the British Pharmaceutical Industry analyse price differences between cohorts of newly launched medicines in the UK and other countries. Their price indices for each country are adjusted by using the Paasche index provided in the same document on p. 198. Note that this Paasche index was calculated for 100 molecules that were off-patent in 2000 and does therefore not represent exactly the NCEs cohorts analysed for patented product prices. However, the UK generics market has been mature for a long time, so we assume that the trend in branded product prices is not significantly different from the trend in generic prices. In addition, the Paasche index includes a combination of patented and generic molecules for most years.

- In addition, Kanavos (2001 and 2002) asserts that the product mix of total pharmaceutical expenditure in Europe is changing towards newer and more expensive products.¹¹⁶ In 1997, the average contribution of recent products to total sales of the top 100 global corporations in Europe was only 16% compared to 32% in the US.¹¹⁷ In 2002, the largest European pharmaceutical company GlaxoSmithKline reported that sales of new products accounted for 27% of its total European sales.¹¹⁸ In addition the (unweighted) average market share of new drugs in the five major European markets France, Germany, Italy, Spain and the UK was 23% in 2001, lending some support to the statement that the mix of total pharmaceutical spending in Europe is changing towards newer products. As shown in Figure 47, new medicines accounted for almost 30% of total pharmaceutical sales in Spain in 2001. In the UK, where generics are traditionally a strong force, the market share of new medicines was only 16% in 2001, but in Germany, another generic-friendly country, it was almost as high as in Spain, close to 25%. In combination with strong overall growth in demand

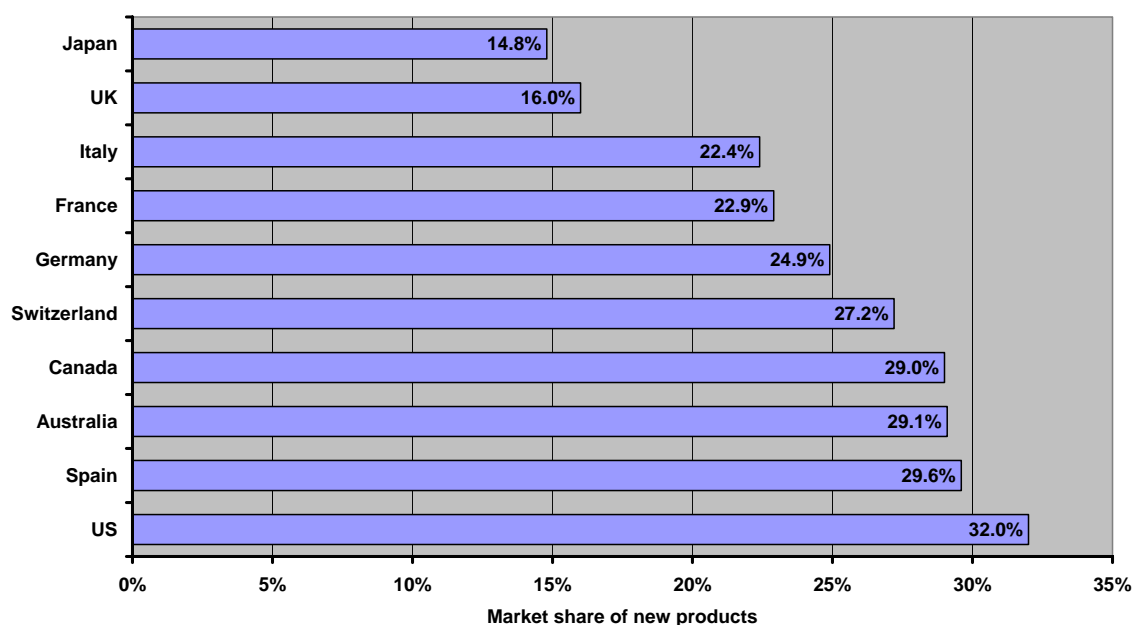
¹¹⁶ Kanavos (2001), p. 3, and Kanavos (2002), p. 27.

¹¹⁷ Gambardella, Orsenigo and Pammolli (2000), p. 35. Recent products are defined as NCEs launched between 1988 and 1997.

¹¹⁸ Datamonitor (2003).

for medicines and continued growth in pharmaceutical market value as forecast by market researchers, the high share of new medicines indicates that, even if pharmaceutical companies might have to accept price cuts per pill for their products, the total pie of pharmaceutical expenditure and especially innovative pharmaceuticals continues to grow.

Figure 47: Market share of new medicines in various countries 2001



Source: IMS World Review, Association of the British Pharmaceutical Industry. Note: new medicines are "products launched between 1996 and 2001".

It is possible that these effects could alleviate the disincentive of restricted prices and/or reimbursement of innovative drugs on innovation to some extent.

8.8 Summary

In this section, we have identified a variety of regulatory factors and their impact on the incentives to innovate:

- **Price regulation and parallel trade:** Almost all European countries have introduced cost containment measures in the last few years, including price cuts and freezes for patented products. Given that these measures were implemented quite recently, it is unlikely that they have had an effect on the current level of innovation. However, since they directly put downward pressure on industry profits and hence the returns to innovation, tougher price regulation and parallel imports are likely to reduce the incentives to innovate in the future.

- **Growing importance of generics:** Even countries that have not traditionally had a strong generics market, such as Spain and France, have recently introduced rules to encourage generic competition. Hence, the returns to innovation and the incentive to innovate are reduced. Given that many European countries have had strong generics markets for several years, e.g. the UK and Germany, it seems likely that this effect has already impacted on the level of innovation we currently observe. Strong generic competition is likely to have two secondary, longer term effects. First, the higher importance of the branded period will provide an incentive to channel resources into R&D for new products that will gain acceptance quickly in order to keep a competitive product portfolio. On the other hand, it will increase the incentive to focus on incremental innovations that will lead to a further period of market exclusion.
- **Therapeutic reference pricing:** By reducing the price premium that first products in a new category traditionally enjoy in many European countries, therapeutic reference pricing for patented products will reduce the returns to innovation and hence the incentives to invest in R&D. Since therapeutic reference pricing has only recently been introduced in some EU Member States, it is unlikely that it has already had an effect on the current level of innovation. In the longer term, by rewarding products that are not in a reference price group, therapeutic reference price systems could contribute to a more efficient allocation of R&D resources to truly innovative products, similar to the effect of the fourth hurdle and cost-effectiveness studies described below.
- **Data protection and market exclusivity period:** Granting extended data protection and market exclusivity periods for significant new indications of already existing products or products for certain groups of patients, such as children, the returns to innovation are increased and hence the incentive to invest in R&D in such products strengthened. The European programme for orphan drugs was only recently introduced and the paediatric programme is still in preparation, so they cannot have affected the current level of innovation that we see today. However, they are likely to positively influence R&D in the future.
- **Risk-sharing:** In principle, risk sharing between producers and health care regulators and/or providers could either raise or lower the incentive to innovate, but in the current climate of cost containment in Europe, risk sharing is often used in an asymmetric way to limit the potential cost to health care providers of a successful product. If used in such a way, risk sharing measures will likely dampen the expected returns to innovation and hence the incentive to innovate. In any case, it seems unlikely that risk sharing schemes have had a significant effect on the incentives to innovate in the past or will do so in the near future.
- **Cost-effectiveness measures:** Cost effectiveness studies could increase R&D costs by requiring the collection of additional data on products' pharmacoeconomic value. An increase in costs will clearly reduce the incentive to invest in innovate products. However, by providing incentives for pharmaceutical companies to invest in R&D for cost effective products with a true social benefit, cost effectiveness requirements are likely to increase the efficiency of R&D allocation. Cost-effectiveness measures are

increasingly being introduced by European countries and are therefore likely to affect the incentives to innovate in the future.

- Location of R&D: Companies have an incentive to invest more R&D resources in countries where the expected returns to innovation are higher. Given that e.g. cost containment measures in the European Union are increasingly putting pressure on returns to innovation, R&D is increasingly moving to other markets, especially the US. As far as location of R&D within the European Union is concerned, the UK seems to attract far more R&D resources than the other two major markets France and Germany, possibly reflecting strong national pharmaceutical companies such as GSK and the UK government's explicit attempts to attract R&D pharmaceutical companies.

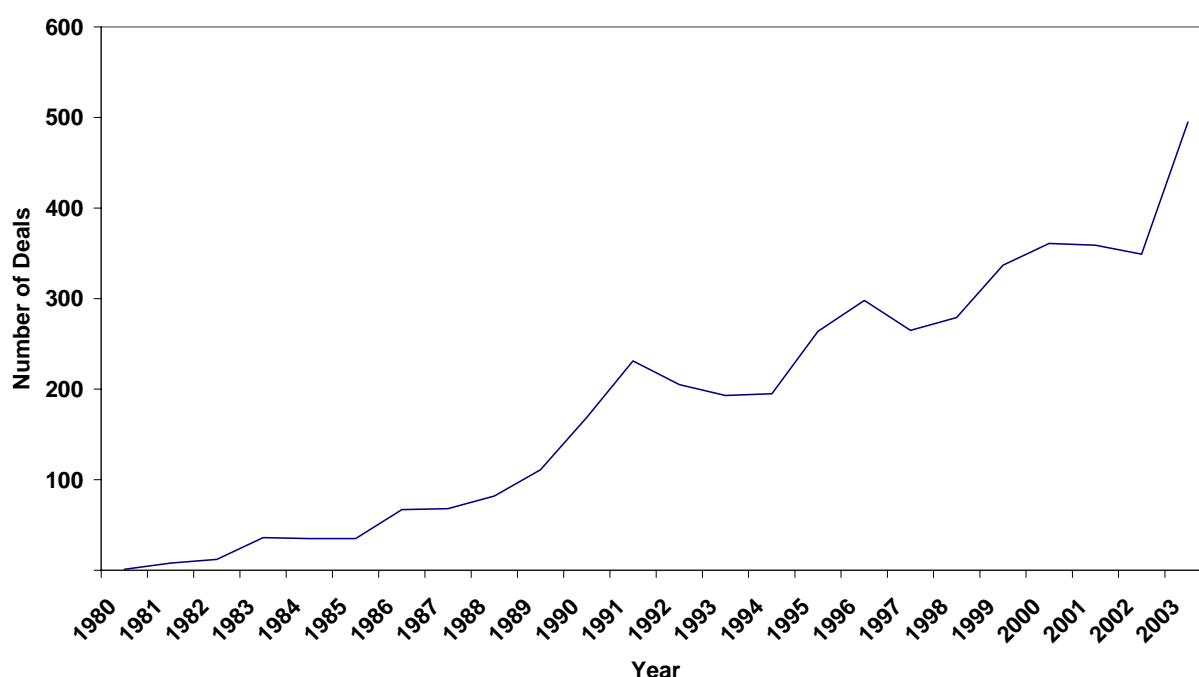
Our analysis of the empirical evidence related to the above-mentioned factors suggests that while prices of newly launched drugs are not increasing in Europe, the share of new drugs in total pharmaceutical expenditure is growing. In addition, population ageing and growth contribute to a situation in which pharmaceutical expenditure and hence the total pie available for pharmaceutical companies continues to increase. Market researchers expect the European pharmaceutical market to grow by an average of 5.2% per year between 2002 and 2007. In combination, these two factors – an ageing population and a greater share spent on new products in the product mix – are likely to positively affect the incentives to innovate in the future by increasing the potential returns to innovation that R&D pharmaceutical companies can obtain.

We find only limited evidence of the effectiveness of cost containment measures before the late 1990s and therefore these do not seem likely to have resulted in a reduced incentive to innovate. It therefore seems unlikely that this was responsible for the fall in authorisations over the last few years. We assess that the factor that is having the greatest impact on expected revenue for new drugs is the increase in generics competition and this may be resulting in a diversion of effort to maintaining revenues. There is, however, a clear concern that encouraging more intense generic competition, without an increase in prices during the branded period will lower the returns to innovation in the future.

9 Phase II: Industry restructuring

The pharmaceutical and biotechnology industries are known for sizable consolidation through mergers and acquisitions in the past ten years.

Figure 48: Total number of worldwide pharmaceutical deals

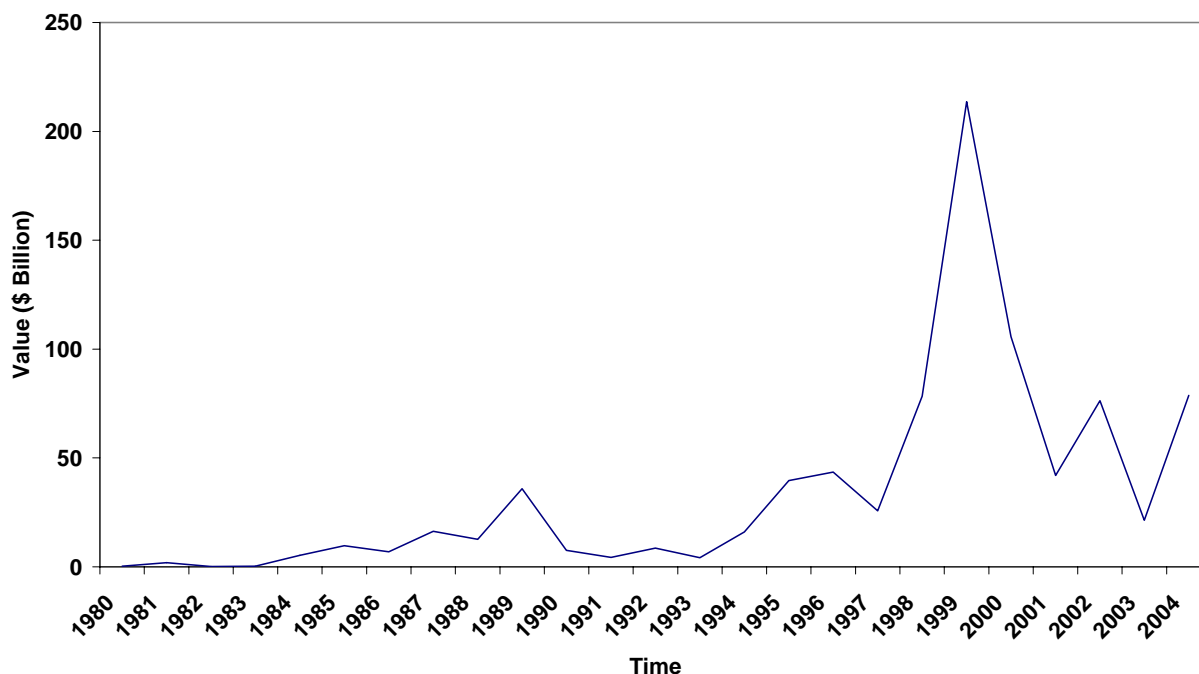


Source: CRA Analysis using Thompson Financial Data. This excludes equity carve-outs, exchange offers and open market repurchases. The date is the announcement date.

As demonstrated in the above chart, the past decade has seen a steady and significant increase in the number of pharmaceutical deals. The average year now sees about two to three times the number of deals made at the beginning of the 1990's.

The situation looking at the value of deals is more complex. The statistics are influenced by a handful of mega-deals that dominate all other M&A activity, and their occasional nature can lead to a very uneven aggregate time trend. Nevertheless, as shown in Figure 48 there is still a striking upswing in deal activity towards the end of the 1990's.

Figure 49: Total value of worldwide pharmaceutical deals (billion dollars)

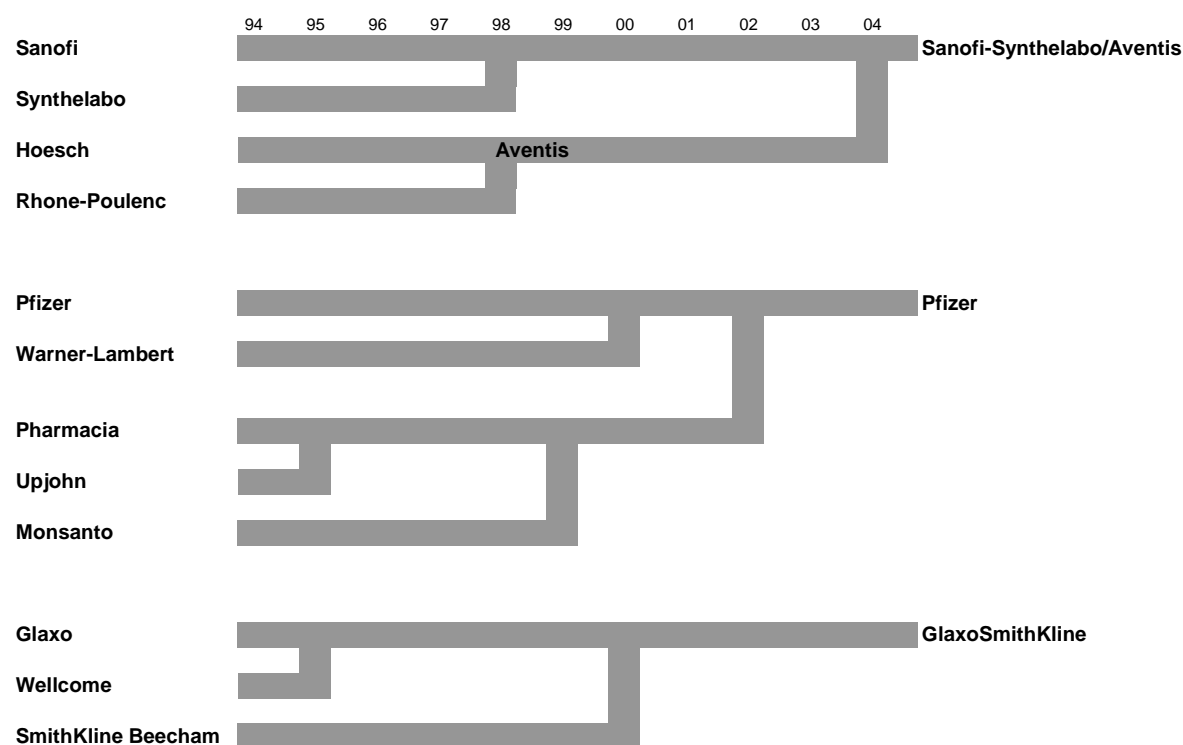


Source: CRA Analysis using Thompson Financial Data. This uses the ranking value including the net debt of the target; excludes equity carve-outs, exchange offers and open market repurchases. The date is the announcement date. Note that the takeover of Aventis by Sanofi Synthélabo is not included.

It is interesting to note that consolidation happened more at the upper end of the firm size distribution. An investigation of 383 mergers found large firms (>\$1 billion market value; 213 of the total sample) more likely to merge than smaller firms.¹¹⁹ This finding is also underpinned by the observation that the largest firms in the pharmaceutical market grew by sequential mergers and acquisitions (see Figure 50).

¹¹⁹ Danzon et al. (2003)

Figure 50: Sequential mergers and acquisitions of the three largest pharmaceutical firms



Source: CRA

The figure shows all mergers and acquisitions with a transaction value of over \$10 billion leading to the three largest global pharmaceutical firms (measured in turnover).

The merger activity of the largest firms lends some support to the conjecture that the industry restructures, with a larger number of small research outfits and few large marketing outfits.

9.1 Merger motives

What has caused this merger wave? One hypothesis is that the necessity to restructure after a period of exceptional growth and profitability during the 1980s and the beginning of the 1990s, was a driving factor. During this period market value of pharmaceutical firms increased three times more than the stock market index. This situation changed in the early 1990s:

“Enhanced buyer power, increased competition from generic and “me too” drugs, the rise of biotech as an alternative research approach, increased government pressure, rising research cost, and a rash of major patent expirations dramatically changed the growth and profit outlook of pharmaceutical companies.”¹²⁰

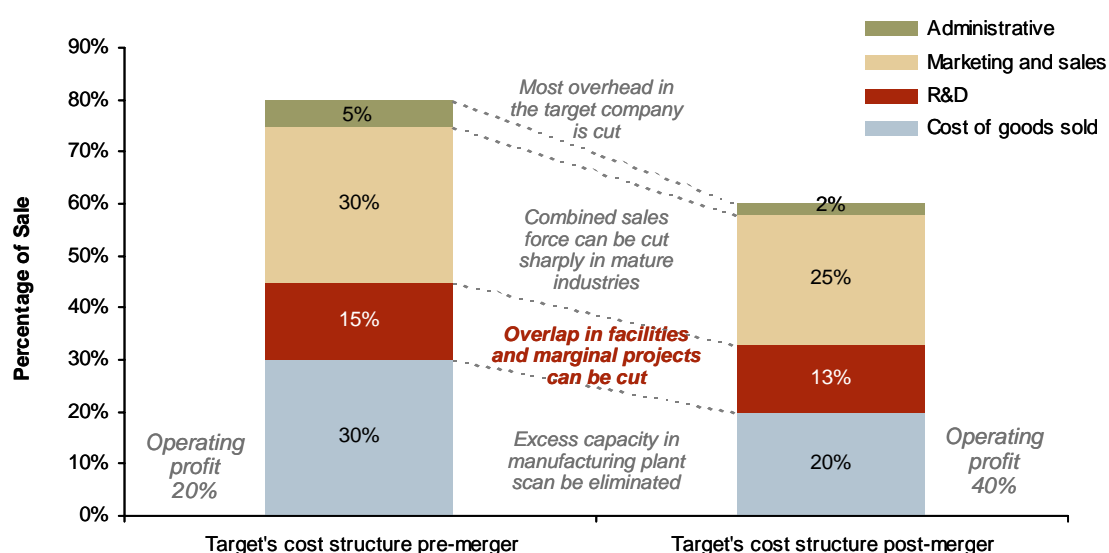
¹²⁰ Ravenscraft and Long (2000), p. 288; similar factors are cited by Balto and Mongoven (1999).

It was argued that during the period of profitability and growth the firms built up organisational slack and inefficiencies. The mergers were seen as a possibility to address these issues by

- Using the shake-up of the merger and the resulting re-organisation of the firm to reduce capacity and cut costs.
- Adding marketed and pipeline products to improve capacity utilisation and smoothing of financial revenues due to anticipated patent expirations and gaps in the product pipeline.

Indeed, cost cutting and the exploitation of economies of scale and scope seems to have been one of the main drivers of industry consolidation. Figure 51 shows the main sources of efficiencies from a horizontal pharmaceutical merger.

Figure 51: Merger efficiencies in horizontal pharmaceutical mergers



Source: Ravenscraft and Long (2000), p. 313.

The figure shows that the most important sources of efficiencies result from the elimination of excess capacity in manufacturing plants (reduction in the cost of goods sold from 30 to 20 percent of sales) in the combination of sales force (reduction in the cost for marketing and sales from 30 percent of sales to 25 percent). Note that these savings can stem from economies of scale. Often it is argued that the combination of more drugs would improve the sales force's ability to gain access to more doctors, thereby increasing sales. For example, in the Aventis merger it was hoped that combining the marketing organisations of the companies would lead to a much stronger presence in the United States.¹²¹ Cutting overhead would only lead to cost savings of 3 percent and the elimination of overlap in facilities and

¹²¹ James (2002), p. 304.

marginal products 2 percent. This supports the conjecture that R&D savings are not the driving force of mergers. Nevertheless, according to these estimates R&D would be cut by over 12 percent.

The importance of cost savings as a merger motive is also underpinned by the large number of layoffs that followed the mergers. Ravenscraft and Long report for eight large horizontal pharmaceuticals mergers that occurred between 1989 and 1996 estimated headcount reductions in the range of 8 to 13 percent of the total headcount (with one outlier with 20 percent).¹²² Similar figures have been reported for later mergers. Cost saving measures do affect research:

- After the merger in 1996 GlaxoWellcome eliminated or put on hold marginal research projects and closed Wellcome's main UK research facility in Beckenham (1500 scientists and staff) and the firm sold manufacturing and research sites in France, Italy, and Spain.¹²³ The cuts were interpreted as a substitution of internal for external R&D.¹²⁴ Moreover, the loss of staff may have been greater than wished: "Several interviewees suggested that GlaxoWellcome lost more talent than they expected. In part this was due to the generous nature of the retirement and severance pay".¹²⁵ Under US law these payments had to be offered to all employees. Analysts estimated that as a result of the disruptions to research programmes by the integration process some parts of the research efforts were delayed by two years.¹²⁶
- Aventis was the result of a 1999 merger of Hoechst Marion Roussel and Rhône-Poulenc Rorer. R&D projects were cut based on a prioritisation that made use of financial criteria. One R&D facility was closed. After the merger the global drug development, regulatory affairs, market and business development was located at Bridgewater in the United States: "This reflected the importance of the US market to the company's business strategy, the importance of the USA as a site for clinical studies and the importance of licensing and partnerships to access US biotechnology capabilities".¹²⁷

Most of the cost savings described in this section would not be classified as merger specific by competition authorities, i.e. they could have been achieved through other means. However, the case study literature describing the mergers often refers to the ability to "start from a clean slate", "take a fresh look at the organisation".¹²⁸ M&A can help firms to "reconfigure their resources, routines and capabilities in the face of the strong inertial forces that constrain their actions thus allowing them to adjust to their changing business environment".¹²⁹

¹²² Ravenscraft and Long (2000), p. 312.

¹²³ Ravenscraft and Long (2000), p. 315; James (2002), p. 303.

¹²⁴ Ravenscraft and Long (2000), p. 315 and 317.

¹²⁵ Ravenscraft and Long (2000), p. 320.

¹²⁶ James (2002), p. 303.

¹²⁷ James (2002), p. 305.

¹²⁸ E.g. Ravenscraft and Long (2000).

¹²⁹ James (2002), p. 300.

9.1.1 ADDRESSING THE PATENT EXPIRY

The expected patent expiry is often cited as a merger motive. Two factors may play a role here. First, patent expiry would lead to a reduction in sales of the blockbuster drug, leaving existing capacities under utilised. A merger can be used to address this issue by smoothing the product profile or by using the merger to eliminate excess capacity. Second, in the pharmaceutical industry even large firms may rely on very few products for their cash flow. However, internal funding of R&D is important since raising external funding is often complicated by problems of asymmetric information (that is the potential investors know significantly less than those in the company) and issues of moral hazard.¹³⁰

In the early 1990s many pharmaceutical companies were still having a significant cash base but the future cash flow was expected to decline due to the factors listed above. Smoothing the cash-flow to allow future financing of R&D is one objective of acquisitions. "Pharmaceutical firms flush with cash from past R&D successes could purchase products by taking over other companies cheaper and faster than they could through internal R&D".¹³¹

9.2 Effects on innovation

Some commentators suggested that the effect of the recent merger activity on innovation was negative. For example, the FDA states as factors contributing to the decline in new product applications:¹³²

- The FDA has observed that mergers within the industry may be causing elimination of candidate drugs that are within the same class. This phenomenon would decrease the number of "me-too" drugs submitted.
- European regulators, facing a similar trend, have cited recent mergers as a factor: merged entities select only the most promising prospective "blockbusters" for further development. The net result of a corporate merger on the size of the company's product pipeline is described as, "Twenty plus twenty equals twenty".¹³³

Consolidation may affect the level and nature of innovative activity through a number of interrelated channels. One possible categorisation is:

- Pipeline consolidation and diversification;
- Disruption due to the integration process;
- Positive knowledge spill-over effects and economies of scale and scope; and

¹³⁰ Danzon et al. (2003). The problems of asymmetric information and moral hazard relate to the fact that an external investor usually cannot fully monitor (and probably not understand) the R&D process that takes place within the company.

¹³¹ Ravenscraft and Long (2000), p. 296.

¹³² <http://www.fda.gov/bbs/topics/news/2003/beyond2002/report.html>.

¹³³ <http://www.fda.gov/bbs/topics/news/2003/beyond2002/report.html>.

- Reduced or increased competition for innovation.

In order to analyse the role of the recent M&A as an explanation for the development of innovative activity we will discuss each of these channels.

9.3 Pipeline consolidation and diversification

It is interesting to observe that two apparently contradictory motives for mergers in the pharmaceutical industry are discussed.

- First, product portfolio rationalisation and the spin-off of non-core R&D assets are often cited as a cause for a deal (see discussion of motives in Section 9.1). Newly combined entities might cast off any duplicative products in development.¹³⁴ Any redundant compounds may not necessarily be licensed to other manufacturers, as this would be tantamount to creating your own competitor.
- Second, the lack of a diversified pipeline and the need to improve drug output and to replace products going off-patent has often been cited as a rational for a merger (see Section 9.1).¹³⁵

In practice, both motives play a role and to some extent complement each other as divestitures of non-core assets are used to finance and prepare for easier integration in later mergers. Moreover, past mergers create the need to re-focus the development effort of the combined firm.

Pharmaceutical companies focus on relatively few therapeutic categories: 80 percent of companies with products in the NDA pipeline focus on four or fewer distinct different therapeutic categories.¹³⁶ This focus on certain R&D categories creates risks, which may have contributed to the desire to diversify. In an analysis of the trend in diversification DiMasi finds a general increase in diversification over time, where diversification was measured as the concentration of the number of NCE approvals of a firm with respect to therapeutic categories.¹³⁷

Diversification may lead to economies of scale and scope and more efficient use of the existing knowledge base (see Section 9.5 below). Thus, it may improve innovative activity. However, managers may also seek diversification in order to reduce the risk of failure of their own firm. While this motive is understandable from the point of view of the managers, it may lead to mergers and acquisitions that are not driven by efficiency considerations and may not create social value. On a different level the conglomerate merger wave during the 1970s may serve as a warning. During this time it was fashionable among managers to diversify their

¹³⁴ PriceWaterhouseCoopers (2001), p. 7.

¹³⁵ See Van Arnum (2003) and Higgins and Rodriguez (2003).

¹³⁶ Higgins and Rodriguez (2003), p. 10.

¹³⁷ DiMasi (2000), p.1185.

companies, a move that was reversed later when many of these mergers turned out to be unprofitable.

Thus, while it is possible that there is, from society's point of view, an excessive desire of managers to diversify, the smoothing of cash flows and the greater focus on potentially successful products is likely to lead to long term benefits of mergers.

Rationalisation and the elimination of duplicate or marginal research programmes that follow a merger may have an immediate negative consequence. To the extent that this is not prevented by competition authority, which insists on divestiture or licensing of overlapping research (see Section 9.6), this would have a negative short run effect.¹³⁸

9.4 Disruption due to the integration process

The integration of the newly acquired assets from consolidation might distract manufacturers from R&D. According to this hypothesis the recent increase in M&A activity would reduce the R&D productivity of companies.¹³⁹

Silvio Claudius Gabriel, at the time CEO of Novartis listed the following potential costs of a merger.¹⁴⁰

- Loss of employees;¹⁴¹ and
- Reduced productivity due to discussions over the merger, fear of job losses and cultural dissonances.

However, he also argued that the disruptions were short-lived and that the main factor of success after the first integration phase was the growth through innovations (and less the development of existing products). The share of new products in total revenues grew from 6% in 1997 to 16% in 1999, three years after the merger.

Moreover, consolidation across different types of firms (e.g., pharmaceuticals and biotechnology) might require additional time to combine technologies, study the results, and implement R&D activity.

¹³⁸ The transfer of R&D programmes is not always straightforward and firms may under some circumstances have an incentive to disrupt the process. Competition authorities have used monitoring trustees to ensure that the acquiring firm becomes a true competitor in the field.

¹³⁹ Challenger (2003) and Firn (2002).

¹⁴⁰ Gabriel (2000).

¹⁴¹ Gabriel quotes as a success that they could convince 70% of the staff in one German location to another location in Germany (500km apart), which was chosen after the merger of Sandoz and Ciba-Geigy.

In order to increase the chances of success, pharmaceutical companies often form alliances before the merger in order to reduce information asymmetries and improve the ability to predict the likelihood of successful post merger integration.¹⁴²

Researchers have argued that a firm's absorptive capacity is based on its own internal research and development efforts.¹⁴³ This means that the acquiring firm needs to provide the same productive environment as the company that is acquired.

Mergers and Acquisitions in pharmaceuticals often lead to a reconfiguration of research teams or the setting of new objectives and internal processes. Moreover, past relationships and ties to the existing firm may be devalued as a result of the post merger integration process. Thus, holding on to the scientists is seen as a major challenge in a merger of pharmaceutical firms. In order to provide incentives to remain with the firm, earn outs or milestone payments are used to incite the researchers.

From a macro view the loss of researchers may not be harmful if they continue to do research as effectively in other organisations. There appears to be little systematic research on the direct effect of the restructuring on the number of scientists active in research. However, some observers point out that a number of researchers switched to less productive positions (if any) after the disruptions of the merger processes, a move that may have also been facilitated by generous retirement plans.¹⁴⁴

The importance of human capital for innovation is also underpinned by findings that the measures that increase human capital (skilled personal) are complementary with all the other policy variables to increase innovative activity in almost all innovative industries. Increasing the level of human capital would increase the intensity of innovation of those firms that innovate and increases the total number of innovating firms.¹⁴⁵ The importance of human capital and knowledge sharing is also illustrated by the finding that there is a significant positive relationship between drug discovery and co-authorship of scientific papers of pharmaceutical company scientists and academic researchers.¹⁴⁶

The management of different cultures is often cited as a critical problem. It was cited as one of the main causes for the bad performance of Pharmacia, where US, Swedish and Italian subcultures were continued after the merger. Aventis faced the challenge of integrating German, French, and American business cultures.

While it is possible that disruptions during the post-merger integration process may lead to a loss of scientists and divert management attention, it seems unlikely that this would affect

¹⁴² Higgins and Rodriguez (2003). These authors argue that acquisitions that follow an alliance are more successful than those that did not.

¹⁴³ Cohen and Levinthal, (1989).

¹⁴⁴ Interview Efpia.

¹⁴⁵ Mohnen and Röller (2000), p.22.

¹⁴⁶ Henderson and Cockburn (1996)

products, which are already very advanced in the pipeline. Finally, unless there is a true cultural clash in the merged entity, we consider these effects as being limited in time, affecting companies in the two years after the announcement of the merger. With these qualifying remarks, it is, however, possible to clearly determine that during this time the effect of the merger activity on innovation is negative.

9.5 Positive knowledge spill-over effects and economies of scale and scope

It is possible that consolidation activity actually stimulates innovation. If there are knowledge spillovers from the therapeutic categories in which the consolidated company is active, then consolidation might actually increase the efficiency of drug development.

One extensive econometric study, which covered about 25% of the pharmaceutical research conducted worldwide in the mid 1990s, found that:

- Larger firms have an advantage in conducting research: Other things equal, research programmes in larger firms were found to be significantly more productive than rival programmes located in smaller firms.
- This advantage was attributed as much to economies of scope as to economies of scale. Benefits of scope arise from the ability of larger firms to internalise information externalities of research that is going on within the firm and of the use of the knowledge capital that has accumulated in the past. Economies of scale arise from specialisation and the sharing of fixed costs.¹⁴⁷

Indeed, the effort to become more efficient and reduce costs in response to increasing pressure from large buyers to reduce the rate of price increases is sometimes cited as the prime reason for consolidation.¹⁴⁸

Some of the merger activity but also the move to form alliances is explained by the advances in biological sciences and the emergence of biotechnology, which made it possible to base the R&D activity more on “science” than on “random” drug discovery methods.¹⁴⁹ It is also argued that the increased importance of science has reduced the value of scale and lead to new small firms entering the market, often based on collaboration between scientists and professional managers. These entities have often been successful in research, then looking for a partner to market the products.

¹⁴⁷ Henderson and Cockburn, (1996).

¹⁴⁸ Balto and Mongoven (1999).

¹⁴⁹ Lacerata (2000).

The need to benefit from knowledge spillovers is also confirmed by the increasing number of Research joint ventures. While these can reduce innovation competition between pharmaceutical companies, they may well increase innovation competition if the R&D would not take place in the absence of the joint venture and the risk of the R&D expenditure would be too great for a single firm.

Overall, it is very difficult to judge the long-run effect of the merger due to positive knowledge spillovers and economies of scale and scope. Some tentative conclusions are possible. First, it seems clear that with the emergence of smaller biotech firms and their innovative performance the institutional world between markets and hierarchies has become much richer. These changes lend some support to the hypothesis that firms may use mergers to adapt and thereby enhance their long-run research capabilities. However, having in mind the primary motive of many mergers in the industry (cutting cost and improving capacity utilisation) this does not appear to be the main driving factor for the M&A activity.

9.6 Reduced or increased competition for innovation

If a merger eliminates a potential (rival) innovator it will directly affect the incentives to innovate and, potentially, the timing of innovation. However, determining whether the effect on the incentives to innovate is positive or negative is not trivial. Although economic theory provides intuition on the different trade-offs, there are no robust general results as to the net-effect of consolidation.

In order to understand the economic effects of consolidation it is helpful to consider the process of innovation as race to first file a patent or to first launch a product. The following factors are important when assessing the impact of a merger on the incentive to innovate:

- A merger affects each firm's probability of winning in the innovation race. This has a positive effect on the incentive to invest in R&D as it increases the expected return on investment. Thus, seen in isolation, this effect is likely to increase innovation.
- However, if several firms pursue different routes to finding a therapeutic advancement, eliminating an independent line of research will increase the expected time until the discovery is made by some firm. This increases the expected time of the research period and therefore the cost of R&D. It also means that patients wait longer for discoveries.
- A merger may affect the value of the "price" in the innovation race. By eliminating a rival post launch competition, e.g. with me-too products, the expected return on investment increases, which in turn has a positive effect on the incentive to innovate.
- Vertical mergers may lead to the exclusion of rivals at one vertical level, which will hamper the incentives to innovate of the excluded firms. Thus, the future distribution of patents and the importance of patents as inputs for competitors may affect the impact of a merger on the ability to foreclose markets.

- Finally, a merger may change the position of the combined research relative to the rival firms. If the merged firm gains significant headway with respect to rival research teams, the latter may stop their research effort.

These considerations show that it is very difficult to make general statements about the effects of a merger or consolidation more generally. A case-by-case assessment is required.

In the recent wave of mergers in the pharmaceutical industry, the European Commission and the Federal Trade Commission (FTC) have generally cleared the mergers but addressed specific competition concerns with remedies. Table 18 shows all pharmaceutical mega-mergers that occurred during the past ten years:

Table 18: Remedies used in selected recent large pharmaceutical mergers

Year of merger	Companies	Remedies imposed by the competition authorities
1996	Ciba-Geigy, Sandoz → Novartis	Licensing, Divestiture
1996	Astra, Zeneca → AstraZeneca	Licensing, Divestiture
1999	Hoechst, Rhone Poulenc → Aventis	Licensing, Divestiture
1999	Pfizer, Warner Lambert → Pfizer	Licensing, Divestiture
2000	GlaxoWellcome, SmithKlineBeecham → GlaxoSmithKline	Licensing
2003	Pfizer, Pharmacia → Pfizer	Divestiture
2004	Sanofi Syntélabo, Aventis → Sanofi Synthélabo	Licensing

Source: CRA Research

The remedies included the divestiture of product lines with overlap and the licensing of

- Inputs for R&D to address foreclosure concerns;
- Products with current overlap to address competition concerns related to drugs already launched; and
- Products where the merging firm has promising R&D.

Given that all mergers went through competitive scrutiny by the European Commission and the FTC, which requested remedies for the specific areas of concern, one view on consolidation could be that it can only have beneficial effects for consumers.

This view may not hold true for four reasons:

- 1) If the merger decisions are viewed as too lenient, the mergers could still have a negative effect on innovation. In this context it is interesting to note that it is sometimes argued that the competition authorities diverged in their assessment of the competitive effects of

these mergers. Moreover, the competition authorities are not only concerned about the level of innovation but also the short-term welfare effects on consumers.

- 2) Competition authorities tend to address specific areas of overlap of existing products or pipeline products and research programmes. Eleanor Morgan who analysed the Glaxo/Wellcome, the Upjohn/Pharmacia and the Ciba-Geigy/Sandoz mergers finds: “Neither competition authority expressed concern about any possible reduction in the general level of innovation in the pharmaceutical industry as a result of these mergers, even in the case of Glaxo/Wellcome, which created the largest pharmaceutical firm in the world”.¹⁵⁰
- 3) It has been questioned whether the remedies related to the research areas with overlap created a competitive situation comparable to the pre-merger situation. The success of R&D depends on a range of factors and an R&D programme cannot be isolated easily. The remedies imposed therefore often included an obligation for the merged firm to provide information and advice to the acquirer of the R&D, including consultation and training by the relevant employees.¹⁵¹
- 4) Finally, competition authorities focus on the incentive effects for the firm as an entity. They do not investigate the potential disruption within the organisations that are caused by the post merger integration process.

Thus, while the scrutiny of competition authorities provides some comfort that the observed merger wave in the pharmaceuticals industry is not the leading factor explaining the current downturn in innovative activities it is not sufficient to disregard the influence of consolidation on innovation. Even if it is argued sometimes that the mergers lead to a reduction in the number of R&D programmes it is not possible to conclude that this has harmed consumer welfare, which also depends on the quality and focus of the innovative activity.

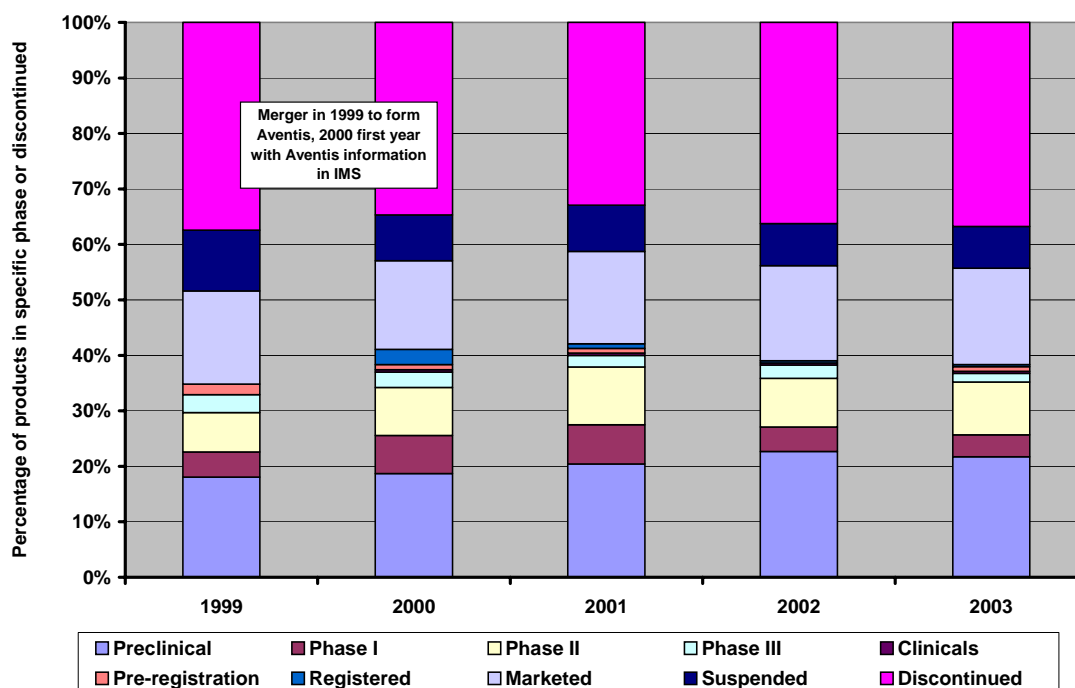
9.7 Empirical evidence

We have used the IMS R&D data already analysed in Phase I of this report to produce evidence on the development of the number of products in the pipeline post merger. See Figure 52 and Figure 53.

¹⁵⁰ Morgan (2001), p. 189.

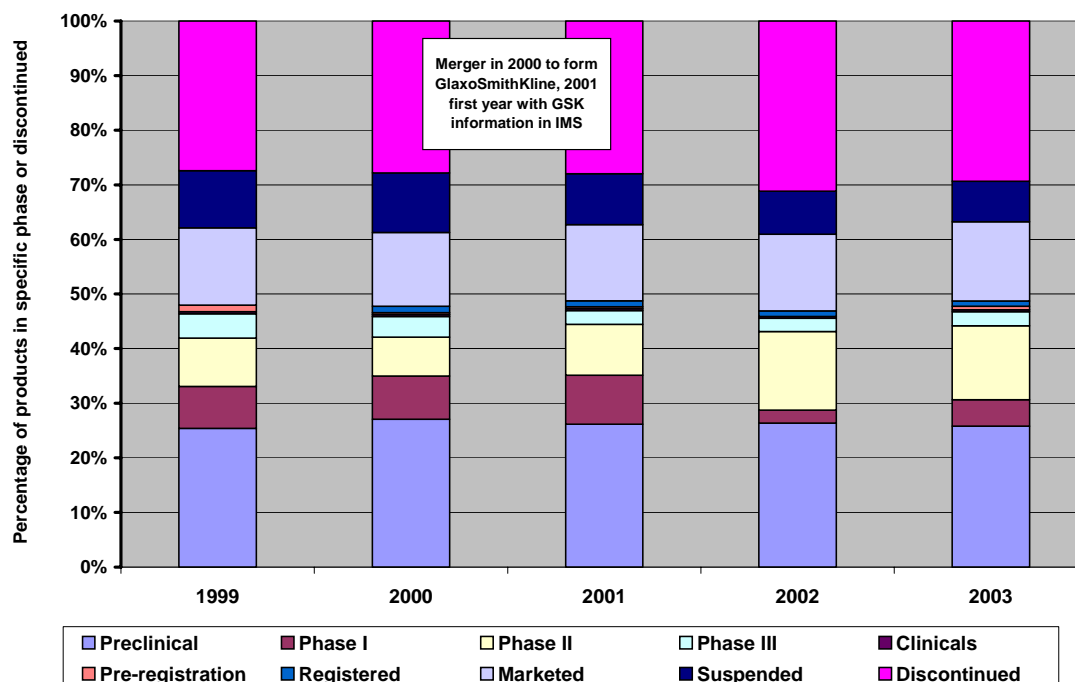
¹⁵¹ Morgan (2001), p.191.

Figure 52: Rhone-Poulenc/Hoechst merger



Source: IMS Health, CRA calculations.

Figure 53: GlaxoWellcome/SmithKline Beecham merger



Source: IMS Health, CRA calculations.

The data show that for the two firms no significant drop in the share of discontinued products can be observed. Clearly, by looking at only two cases we cannot draw general conclusions. A better empirical approach is to

- Use a larger sample of firms and observations;
- Compare the development of R&D to those firms that have similar characteristics (as firms that merge may be more likely to have had a bad (or good) R&D performance even without the merger. We have used the IMS R&D data to analyse the development of the number of products in the pipeline of the merging firms after the Rhone-Poulenc/Hoechst merger and the Glaxo Wellcome/SmithKline Beecham merger. The data shows no significant drop in the share of discontinued products."

A recent empirical analysis has done this based on large¹⁵² mergers and acquisitions¹⁵³ in the pharmaceutical-biotechnology industry during the period 1988 to 2001.¹⁵⁴ They find that it is indeed important to control for prior characteristics that are likely to be associated with future performance. Firms with a relatively high likelihood of merging in a given year experience relatively small growth in sales, employees, and R&D on average, over the following three years. The performance of firms that have merged needs to be compared to that sample.

However, this research has not used the number of products in the pipeline but analysed R&D expenses as a proxy for innovative activity. They find that for large firms¹⁵⁵ the merger had no significant effect on R&D expenses in the three years following a merger. For small firms it is found that there is relatively slow growth of R&D expenditure in the first year after the merger compared to similar firms that did not merge.

9.8 Summary

Since the early 1990s the pharmaceutical industry went through a process of significant consolidation through mergers and acquisitions. While writing this report, another mega-deal is underway. Aventis accepted an offer from a once-hostile bidder, Sanofi-Synthélabo, of 55.3 billion euros (\$65.5 billion). The combined Aventis and Sanofi ("Sanofi-Aventis") will be the world's third-largest pharmaceutical company, behind Pfizer and GlaxoSmithKline, with about \$30 billion in sales in 2003. A number of analysts have argued that this M&A activity may have harmed innovation. Indeed, when looking at the motives of many of the

¹⁵² Large means transactions with a transaction value of at least \$500 million or a transaction where the transaction value represents 20 percent or more of a firm's pre-merger enterprise value.

¹⁵³ Of the 202 mergers considered, 97 were classified as acquisitions (a firm purchased part or all of another firm), 59 as targets (a firm sold a substantial portion or all of itself to another firm), and 46 as pooling (firms pooled their assets or merged with another firm of approximately the same size).

¹⁵⁴ Danzon et al. (2003).

¹⁵⁵ Large firms are those that had a market value of over \$1 billion at least one year during the study period (n=213). Small firms never had an enterprise value of over \$1 billion but had sales of at least \$20 million in at least one year (n=170).

mergers we find that cost cutting was high up on the agenda. We find that four factors suggest a negative short-run effect on the number of pipeline products and research pipelines:

- Although R&D facilities were not the most important target of cost cutting efforts, often selected R&D labs were closed after the combination of the merging firms.
- Further, the elimination of marginal and overlapping research programmes or pipeline products after the merger is likely to have reduced the number of different programmes.
- The disruption of the merger and the combination of different organisational (and national) cultures has led to losses of scientists and cultural clashes that are likely to have disrupted the research process.
- Finally, there are no compensating factors that would suggest that a merger could have an immediate short-run effect on the number of research activities or the research productivity.

We conclude that, if a merger has a short-run effect on innovative activity at all, this effect is likely to be negative. A systematic study of the effect of the pharmaceutical mergers on R&D expenditure confirms this view for smaller mergers (up to \$1 billion market value of each firm).¹⁵⁶ The investigation shows that compared to similar firms the R&D expenditure is significantly reduced in the year after the merger. The sample of large mergers (one firm has more than \$1 billion market value) does not show any effect in the three years after the merger.

It is not within the scope of this project to conduct a similar econometric study with regard to the effect of a merger on the number of products in the pipeline. However, we looked at two large-scale mergers and found little movement in the number of pipeline products that were discontinued, compared to the year prior to the merger.

Thus, overall we found theoretical arguments that the M&A activity would in the short-run lead to a reduction of research and development expenditure and an elimination of marginal research programmes. There is also empirical and case study support for these conjectures.

Determining the long-run effect on R&D, however, is much more difficult. One important motive for the merger activity was the desire to improve the product portfolio and to address the expected drop in capacity utilisation and cash flow following the patent expiry of major drugs. There are a number of reasons why the merger activity may lead to improved long run innovation:

- The elimination of marginal products may have focussed attention on those research projects with the greatest potential. Thus, there may be a quality effect of selection.
- Some analysts suggest that the M&A activity and the shake-up of the organisations were used to re-orient the firms to adapt to a changed environment. In particular, a

¹⁵⁶ Danzon et al. (2003).

different mode of interaction with the highly innovative smaller biotech firms was mentioned as a beneficial effect. Moreover, the combination of scientists, which may be disruptive in the short run, can also lead to positive knowledge spillover effects in the longer run.

- Improvements in capacity utilisation and the smoothing of the product portfolio may have lead to an improved cash flow profile compared to the no-merger scenario and therefore increased the internal funds available for research and development, which largely depends on internal funding.
- Finally, consolidation may also lead to increased competition for innovation. Seeing innovation activity as a race to achieve a patent, a merger may increase each firm's probability of winning the race and also increase the value of the patent as the expected intensity of competition after the product launch may be lower. These effects will tend to encourage investment in innovation and intensify the competition in the "patent race".

There are, however, also potentially negative long-term effects on competition. If the combined entities gain significant headway relative to their rival firms in certain research areas, this may put off rival firms' efforts to innovate in this therapeutic class. Moreover, if a merger leads to an elimination of an independent line of research, the expected time until discovery may be increased, raising the expected cost of R&D. This may potentially lower research effort and may mean that patients would have to wait longer for discoveries. Finally, in particular vertical mergers may lead to foreclosure, excluding rivals on one vertical level.

Competition policy addresses these concerns and almost all large mergers in the pharmaceutical industry go along with divestitures or other remedies designed to address the potentially negative effect for patients.

Given the time lag between a discovery and the product launch, it is, of course, difficult to empirically measure the long-run effect of the merger activity on innovation. However, one stylised fact is noteworthy, the pharmaceutical industry as a whole has continued to increase the amount spent on R&D (in nominal terms) continuously since 1980, although the growth rate has experienced some volatility and a downward trend. Still, this together with the dynamics of the industry, which is also reflected in the biotech revolution and the emergence of new small firms, and the scrutiny by competition authorities make us hope that the positive long run effects of consolidation will outweigh the negative effects.

10 Overall assessment of Phase II

In this section we summarise the findings of the previous sections in an attempt to identify the most important causal factors for the observed reduction in applications for new active substances observed at the beginning of this century. The results reported in this section were used to inform the roundtable discussion. The feedback that we received enriched the findings and the assessments reported below and the formulation of recommendations in Phase III. We distinguished between the following groups:

- Expected revenue for new drugs;
- Cost of developing new drugs; and
- Industry restructuring.

Some of the factors were identified as having different effects in the short-term than in the long-term. Moreover, some factors are more relevant for explaining current output of innovative products (i.e. they have played a role in the past ten to fifteen years) others are more likely to affect future output as we only observe changes today or in the recent past. A large number of factors, however, reflect trends that have started in the first half of the 1990s and that continue to be relevant today.

10.1 The returns to innovation

The structure by which pharmaceutical products are remunerated is changing dramatically in Europe.

- A combination of cost containment, parallel imports, reference pricing and encouragement of generics is lowering the returns to existing products. However, overall expenditures continue to rise;
- This is increasing the focus on the patent period with three effects: (i) increasing focus on new products (ii) leading to greater efforts to maintain protection through formulation changes or new indications (iii) pressure to maintain pipelines that has resulted in consolidation;
- Subtle changes such as therapeutic reference pricing and the impact of the fourth hurdle of relative cost effectiveness are changing the incentives to win the innovation race, leading to greater focus on differentiation and possibly less focus on being first in category; and
- New regulatory strategies such as extendable data protection and market exclusivity and risk-sharing are encouraging R&D into areas that were previously neglected.

The nature of the European regulatory system is in some way moving towards that of the US. For example, the increasing levels of generic erosion seen in a number of Member States are focusing pharmaceutical companies on the patented period. At the same time, new methods of reference pricing and cost-effectiveness studies are encouraging distinctive products. There is a danger that reduced remuneration of older products does not translate into greater returns during patented period lowering returns to innovation.

With regard to the future, we expect that the cost containment measures that were implemented in the last few years in most European countries – in particular in relation to price regulation and parallel imports, and therapeutic reference pricing – will negatively affect the expected returns to innovation and hence the incentives to innovate for European pharmaceutical companies. On the other hand, we assess that demographic trends, in particular population ageing, and the change in the product mix of total pharmaceutical expenditure towards newer products will positively influence expected returns to innovation and thereby the incentives to invest in R&D. In addition, the new programmes of the European Commission to incite research for orphan and paediatric medicinal products by granting extended data protection and market exclusivity periods are likely to positively influence R&D in these niche areas in the next few years.

10.2 The cost of R&D

Studies showing the increased cost of R&D to bring a product to market are well known. For example, the Tufts analysis shows the cost increased from \$231 million in 1987 to \$802 million in 2001 (or \$897 million including post approval R&D). The general conclusions of these studies are also supported by other research. Although there has been a vigorous debate regarding the level of costs (and whether costs are over stated due to the inclusion of opportunity costs and the types of product selected for analysis) there is little dispute that the costs have risen. In particular, this shows that there has been an:

- Increase in clinical costs relative to pre-clinical costs;
- Increased cost of Phase I relative to other phases;
- Increase in out of pocket expenses even before allowing for product failure rates and the opportunity cost of time.

The increasing cost appears to reflect a number of factors:

- Larger studies: The number of patients needed per NDA has increased from a low of 1,321 in the period 1981 – 1984 to 4,237 for the period 1994-1995. More recent evidence from the CRA roundtable supports this argument with some therapy areas requiring large trials for products to be considered. This appears to, at least partly,

reflect demand by regulators for evidence that products offer material benefits to other products and increased use of the clinical trial data in marketing;

- Intrinsically more difficult therapeutic areas leading to higher costs per patient; and
- Introduction of new technologies: although there are divergent views regarding on the long-term impact of new technology there is general consensus that this has increased costs in the short-term.

We have also reviewed the information on the costs of research and development to understand the trend for R&D to grow faster in the US, seemingly at the expense of Europe. There appears to be a number of concerns regarding the ability to innovate in Europe:

- Costs relative to Eastern Europe: The contract research organization market in Europe is \$2.6 billion compared to \$4.18 billion in the US. The market in Europe is expected to grow to \$4.26 billion by 2007, however, as firms move to Eastern Europe. Eastern European contract research organisations (CROs) benefit from low cost patient reimbursement. Patients in the region tend to be under medicated, which reduces the risk of patients using competing medications and compromising the integrity of final data.
- Technology focus: "...the relative position of the US as a locus of innovation has increased over the past decade compared to Europe. Moreover, the overall picture suggests that Europe's performance is comparatively worse in biotechnology." In Europe, the pharmaceutical industry has not effectively applied new technology to become specialists in particular areas, which US firms have done. This is not a cost issue. Indeed on most measures of cost undertaking them in Europe is considerably cheaper. This appears to reflect the structure of the scientific community and perhaps the desire to undertake research in the market, which represents the greatest return.
- Structural barriers: it has until recently been the case that a successful study in the US was easier to use in Europe and the rest of the world than a European study. Equally, a study undertaken in the US can be used everywhere in the US, whereas, there were still reservations regarding studies undertaken in some parts of Europe being used in others. Therefore the cost effectiveness of studies in Europe is lower.

The analysis of the cost of developing new drugs clearly shows an increase in the real cost of developing new drugs. We find that the increase of the complexity of the products, the increase in the size of the clinical trials may have affected innovative activity in pharmaceutical companies. Moreover, the shift to new research technologies has lead to an increase in cost and a lowering of research productivity in the short run. We expect this effect to be reversed in the future, when the impact of biotechnology on innovative output will come through. We do not find that the authorisation process is a major explanatory variable.

10.3 The nature of competition between pharmaceutical companies

There was a significant increase in merger and acquisition behaviour during the 1990s. There is some evidence that this is leading to a polarisation of the pharmaceutical industry – giant marketing companies and smaller R&D companies. This is consistent with the increased alliances and licensing agreements seen throughout the pharmaceutical industry.

In the short-term, there are four theoretical reasons why mergers may disrupt innovation. We therefore conclude that mergers are likely to have been a contributing factor behind the fall in new products in late 1990s and early 2000s. In the longer term, theory alone provides little guidance.

- Positive impact on innovation through the removal of duplicative me-toos, spillovers, increased scale, smoothed financing and greater incentives to innovate.
- Negative effect on innovation through the reduction in competition in particular therapeutic areas and the removal of competing products.

The competition authorities are addressing the potential negative effect of any diminution in effective competition by imposing constraints at the time of the merger. In fact, many of the recent mergers in the pharmaceutical industry were only cleared by the competition authorities under certain conditions, e.g. divestitures and the licensing of products to other companies. Moreover, there is no clear evidence that competing products were removed from the market.

Mergers appear to be motivated by a desire to cut costs and adapt to a changed environment rather than an attempt to reduce competition. They inevitably lead to a short-term disruption in innovation but it is less clear that they have any long-term negative effect, indeed, they may encourage innovative behaviour.

11 Phase III: Recommendations

The previous sections of this report have focused on answering the questions of whether there is a worldwide crisis in pharmaceutical innovation and identifying the range of factors that have played a part in the recent fall in applications and authorisations and the longer-term reduction in the productivity of innovation.

Based on the analysis of the first Phase of our project, we believe the low level of authorisations observed in 2002 and 2003 was unusual and does not in itself warrant particular intervention. Without any particular regulatory action we would expect the number of new active substances to return to the level seen over the last ten years.

Instead, the focus should be on the longer-term global issues regarding the reduced productivity of innovation and the delay in the benefits arising from new technologies. There are also particular issues that relate to the location of innovative activity in Europe.

There are a number of policy proposals already set out in the revised EU pharmaceutical legislation that are likely to improve the incentives to innovate.¹⁵⁷

- *Faster market access for products offering significant therapeutic benefits through the accelerated procedure and the possibility of conditional approval for breakthrough treatments.* These measures will bring forth innovation by increasing the returns from truly innovative products although – given the wave of product that are still in Phase II – this will not have an immediate effect.¹⁵⁸
- *Streamlining the regulatory process and changing the focus of the EMEA to the provision of scientific advice and support to industry.* This will provide greater regulatory certainty and will facilitate the authorisation process for companies that need to seek advice regarding development issues in particular therapeutic and technology areas. This also addresses one of the concerns regarding fragmentation of the European system.
- *Greater clarity regarding the level of market exclusivity through a harmonised ten-year data exclusivity period (with an additional year granted for innovative research on already marketed products) while allowing generic applicants to prepare for the market before data exclusivity expires (the “Bolar provision”).* These changes increase transparency and consistency across the mutual recognition and centralised procedure, thereby reducing uncertainty related to the returns to innovation. For those

¹⁵⁷ For a detailed description of the review of European pharmaceutical legislation, see Appendix II.

¹⁵⁸ Note however that in exceptional circumstances, e.g. unmet medical need, the current regulatory framework allows for products to be authorised after phase II.

products where data exclusivity would currently be granted for less than 10 years, it strengthens data protection and thereby increases the incentive to innovate.

However, given the long-term reduction in productivity more will need to be done. Based on our analysis of the nature of the problem we set out below the appropriate objectives for European policy over the next five years. This takes into account the many recommendations suggested by the FDA in the US, by the G10 Medicines Group and the European Commission in Europe, and the Ministry of Health, Labour and Welfare in Japan as well as by the industry itself to address the global and regional issues with regard to innovation in the pharmaceutical industry. The objective is to set out the range of recommendations and the priority that should be given to them to allow all stakeholders to focus on some selected areas and make the most efficient use of the limited resources for change and reform that are available.

11.1 Recent policy recommendations

Before presenting CRA's assessment of European priorities for promoting innovation, we first describe some policy suggestions that have come out of various discussion processes worldwide with regard to this issue.

11.1.1 EUROPE: G10 AND THE EUROPEAN COMMISSION

During the last five years, discussion has focused on the competitiveness of the pharmaceutical industry in Europe. Much of this debate had been triggered by reports finding that Europe was "lagging behind in its ability to generate, organise, and sustain innovation processes that are increasingly expensive and organisationally complex."¹⁵⁹ In response to this, the European Commission set up a High Level Group on Innovation and the Provision of Medicines – the so-called G10 Medicines Group – in early 2001, with the task to develop recommendations on how to overcome the problems in the European pharmaceutical industry.

The G10 recommendations were published in May 2002 and ranged from the establishment of benchmarking systems to assess the competitiveness and performance of the European pharmaceutical industry to measures aimed at accelerating product availability (both marketing authorisation and pricing decision procedures), increased information exchange between Member States and the European institutions on assessments of cost and clinical effectiveness, and the creation of European virtual institutes of health to connect the already existing competence centres and overcome the fragmentation of research in Europe.

¹⁵⁹ Gamardella, Orsenigo and Pammolli (2000).

The recommendations also demanded that more attention should be given to creating competitive markets for generics, non-prescription medicines and medicines not reimbursed by the national health systems, and called for measures to increase the incentives for innovation, e.g. through a European database on clinical trials, special policies for orphan and paediatric medicines and the formulation of a European strategy on biotechnology.

The European Commission responded to the G10 recommendations in a Communication in July 2003, indicating how it intends to take the recommendations forward and formulating key action points.¹⁶⁰ In fact, many of the G10 recommendations have already been taken into account in the recent review of the European legislation on pharmaceuticals as described above.

In addition to the already implemented changes, the European Commission intends to follow-up on all other recommendations made by the G10 group, including the efforts to overcome the fragmentation of Europe's research centres, more public funding of R&D, and the creation of a database for clinical trials. Although these recommendations appear to be consistent with our assessment of the problems facing the industry there is a potential problem resulting from focusing on too many policy objectives.

11.1.2 UNITED STATES: THE FOOD AND DRUG ADMINISTRATION (FDA)

The problem of declining R&D productivity and the reduction in the number of innovative medicinal products being authorised in the US has been highlighted in a number of recent FDA reports, the two most significant of which are:

- “Improving innovation in medical technology: beyond 2002”¹⁶¹
- “Innovation – Stagnation: Challenge and opportunity on the critical path to new medical products”¹⁶²

The first report focused on agency-wide initiatives to speed up the development process by reducing delays and costs in product approvals. Particular attention was focused on avoiding multiple review cycles and improving the guidance that was offered by therapeutic group and for emerging technologies.

The second report focused on encouraging a joint effort involving the academic research community, industry and scientists at the FDA focusing on how the process of drug development could be improved to release the benefits of biomedicine. This involved the identification of the critical issues that require action, as well as internal changes at the FDA to both improve the recognition of these issues and to support high-priority critical path

¹⁶⁰ European Commission (2003).

¹⁶¹ FDA (2003).

¹⁶² FDA (2004).

research efforts. This therefore represents a more focused approach on releasing the bottleneck that is currently observed in drug development.

11.1.3 JAPAN: THE MINISTRY OF HEALTH, LABOUR AND WELFARE (MHLW)

In recent years, there has been an increasing recognition that Japan is losing out as a location of research and development and that this may represent a significant lost opportunity given the developments in genomic drug discovery. The policy response to this problem was set out in a paper by the Ministry of Health, Labour and Welfare, entitled “To reinforce the global competitiveness of the pharmaceutical industry, Mainstay of the Century of Life – Vision of the industry”.¹⁶³

In the paper, it is argued that action on a wide number of fronts needs to be taken now to ensure that Japan will benefit from the coming “golden era of new drugs” resulting from genomic drug discovery. In particular, there is a designation of the five-year period 2002-2006 as a period of national “intensive promotion of innovation” with an action plan setting out how to establish and improve the infrastructure necessary for drug discovery.

The action plan covers a wide array of initiatives, ranging from the protection of intellectual property and the encouragement of basic research to improving the link between basic research and drug development (“translational” research), establishing institutes of basic medical technological research, and promoting technology transfers, R&D credits, regulatory reform on authorisation and changes to the pricing and reimbursement system. This clearly offers useful guidance on how other parts of the world are intending to promote innovation but also increases the pressure on European policy makers to make Europe an attractive location for innovative activity.

11.2 CRA recommendations

As noted above, it is generally accepted that policy initiatives need to focus on the bottlenecks in pharmaceutical development. Based on the findings of our study, these currently appear to be in Phase III. Hence, we believe that the most effective way to increase the number of marketing applications and authorisations in the short term will be to clear the bottleneck of Phase III development by helping companies accelerate the process of bringing these products to market. In addition, there are longer-term policies that should receive high priority in order to promote a climate in Europe that is more conducive to R&D and innovation.

Finally, some policies have been recommended in the past that might be difficult to implement in the medium term and whose effect on innovation is to some extent uncertain.

¹⁶³ Ministry of Health, Labour and Welfare of Japan (2002).

Hence, we believe that these policies – although they might be beneficial in the long term – should receive a lower degree of priority when deciding how to best use the available resources to kick-start pharmaceutical innovation in Europe.

11.2.1 CLEARING THE BOTTLENECK OF PHASE III

The first two phases of our study indicate that the recent decline in marketing authorisations and marketing authorisation applications is not due to a fall in the number of products in the development pipelines of pharmaceutical companies. Rather, a higher proportion of these products appear to be in Phase II of clinical development rather in Phase III, applying for marketing authorisation application or getting ready to launch (than has historically been the case). The existence of a bottleneck was confirmed by industry experts during the roundtable held by CRA in June 2004.¹⁶⁴

Clearly, bringing products to the next phase of development is a task that industry is responsible for. Still, regulators and governments can follow some short to medium-term policies in order to help companies to speed up the process of bringing products that are already in the pipeline but held up in Phase II to the market more quickly.

Recommendation No. 1: Focus on the critical path as important for Europe as US

The first recommendation recognises that the application of new technologies has been more successful in terms of identifying possible products in early stages of development, but this has not resulted in reciprocal improvements in later stages of the development process.

Based on the increasing cost of developing products and the fall in the number of authorisations, the FDA has suggested that there is a need for a joint effort from industry, university and research institutes, and themselves to accelerate the development in applied sciences in order to catch up with development in basic research and new technologies. They have called this a focus on the “critical path” between basic research and product development – major steps along this critical path include clinical trial design and the development of appropriate biomarkers that can be used to improve the efficiency of drug development. The next steps of this approach involve (1) the FDA developing a national “critical path opportunities list” identifying the concrete tasks that need to be focused upon; (2) the FDA undertaking consultation on this list from public and private stakeholders; and (3) internal changes to the FDA so that it can support effort in the crucial areas.¹⁶⁵

The potential benefits of focusing on the critical path appear to apply equally to Europe as to the US. In fact a failure to focus effort in Europe is likely to lead to even less European-led pharmaceutical innovation, particularly in the burgeoning areas of genome sciences and

¹⁶⁴ CRA roundtable in Appendix IV.

¹⁶⁵ FDA (2004).

biotechnology. In particular, in the CRA roundtable we discussed how new biomarkers have the potential to speed the availability of medicines to patients if they can also be used for regulatory decision making. Biomarkers are already used to inform development decisions in industry (e.g., for early clinical ‘proof of concept’). There is a progression and continuum from ‘biomarker’ (used as a development tool) to ‘surrogate end-point’ (sufficiently widely accepted to be used as the clinical basis of approval). Historically only a few biomarkers have gained acceptability as surrogate end points (e.g. blood pressure or cholesterol levels in cardiovascular medicine). Therefore the industry needs to work with regulatory bodies to determine how a greater level of understanding on the use of such end points can be established.

To the extent that these activities focus on current bottlenecks in the development process, they would appear to represent high returns in the short to medium term.

Recommendation No. 2: Improved communication between regulator and industry during key phases of development

A second set of policies that can help to speed up the process of bringing products from clinical development to the market is to improve communication between the authorisation authorities and the pharmaceutical companies responsible for designing clinical trials and filing applications for marketing authorisation. Better communication will ensure that companies will be more aware of the requirements of regulators and that regulators might become more aware of problems identified by the industry. One example could be an agreement on using advances in applied sciences as appropriate end-points for a product in development. Another example could be better understanding of the pro and cons of focusing a product’s development on a narrow area where products can be shown to be superior resulting in a quicker review process versus focusing on a wide range of therapies.

In the US, the FDA conducts formal consultation rounds with pharmaceutical companies during Phase II of clinical development. The industry experts at the CRA roundtable indicated that such a consultation process should be implemented in Europe. While there are no plans to introduce a formal consultation round between the EMEA and the industry, the recent review of the EU pharmaceutical legislation indicates a move in this direction. In particular, the review provides for structural changes to the EMEA that are intended to focus the agency’s work on innovation and to reinforce its scientific profile. The EMEA is tasked to increase the provision of scientific and regulatory advice to industry and its committees responsible for marketing authorisations are required to establish standing working parties to provide scientific advice to undertakings. There remains a concern, however, regarding the extent to which the guidance will be agreed in practice or whether the goal posts will change later in the development process.

A number of dimensions have been identified regarding further improving the dialogue between industry and regulators during the development phase in Europe so as to reduce

requests for additional data and regulatory questions following submission. With the goal of increasing predictability of outcomes for marketing authorisation applications, the following should be considered:

- The EMEA's recent 'road map to 2010' proposes establishing 'centres of excellence' in scientific assessment in certain national agencies, coordinated by the EMEA. This could result in significant benefits through the earlier appointment of the Rapporteur and assessment agency allowing pharmaceutical companies to maintain ongoing dialogue with the assessment team during development;
- Increased availability of regulators to provide scientific advice prior to filing;
- Increased use of therapeutic advisory groups, as a forum for regulatory assessors to seek advice from medical opinion leaders, and also for dialogue with companies; and
- Finally, the benefits of formalising the process between the industry and the regulator should be considered. For example, consideration should be given to near-binding negotiated agreements on the requirements for approval of a given medicine, i.e. if the nature of a phase III programme for a medicine is agreed with the regulators in advance and this is completed as planned with positive results, approval should be anticipated without a shift in the requirements post-hoc. This could potentially increase the industry's confidence in using new technologies to lower the cost of drug development.

11.2.2 IMPROVING EUROPE'S ATTRACTIVENESS AS A LOCATION FOR INNOVATIVE ACTIVITY IN THE MEDIUM TERM

In addition to the short-term strategies described above, there are longer-term strategies that should also receive high priority in order to create a more favourable R&D climate and ensure Europe's competitiveness especially vis-à-vis the United States (but also Japan). These policies relate to increasing industry capacity with regard to R&D processes, ensuring reasonable returns to the launch of innovative products, ensuring the vigilant supervision of mergers and acquisitions in the pharmaceutical industry, co-ordinating R&D tax credits, and improving public-private co-operation.

Recommendation No. 3: Addressing fundamentals to prevent future bottlenecks and increase industry capacity

At the CRA roundtable, industry capacity was identified as a potential longer term problem in Europe, in particular the industry's limitations to deal with more than a certain number of products in Phase III at a time. The number of development projects in Europe may partly represent the current capacity level not only with regard to research staff, but also regarding the management of clinical trials and the number of patients willing to participate in clinical

trials. In the longer run, expanding the capacity of industry to conduct R&D requires structural changes and investment in a better infrastructure. This has also been recognised by the Japanese government. The number of clinical trials has fallen in Japan over the last years and the government action plan to increase the competitiveness of the Japanese pharmaceutical industry calls for increased training of clinical research coordinators and the establishment of a better climate for contract research organisations. In addition, the government intends to increase promotional and public relations activities in order to inform the public more about the significance and details of clinical trials and hence to attract more volunteers to participate in trials.¹⁶⁶

In Europe, the clinical trials directive (Directive 2001/20/EC) has established principles of Good Clinical Practice (GCP) that provide for simplified and harmonised administrative procedures relating to clinical trials, aimed at enabling a better level of co-ordination of trials across Europe. Also, a European clinical trials database has been established to enhance communication between regulatory agencies. Interestingly, although the clinical trials directive was intended to harmonise the procedures and increase the incentives to innovate, the industry does not seem to be convinced that it will have these effects. At the CRA roundtable, there was a general feeling among industry experts that the requirements of the directive might reduce (or at least not improve) any advantage the EU currently has with regard to the cost of clinical development compared to the US. The EC should consider whether appropriate investment is being made in the long-term capacity of the European industry to maintain the level of clinical trials and steps needed to maintain Europe's cost advantage. This may involve working with Member States to communicate the need for public participation in drug development.

Recommendation No. 4: Prices during branded period need to sustain incentives to innovate

Section 8.2 of this report discusses the effect of increased generic competition on the incentives to innovate. Encouraging generics while holding prices of branded products constant or even forcing them to fall will reduce the returns to innovation and hence – in the longer run – the incentive to bring new products to the market. Competitive generic markets allow the full benefits of price competition in areas where patents of branded products have expired, this is an appropriate policy for reducing the pressure of drug budgets. However, the encouragement of generics needs to be matched by increased price flexibility during the patented period.

The higher returns to innovation have often been mentioned as one possible reason why many companies move their R&D from Europe to the US.¹⁶⁷ Further, in Japan, falling prices for branded products have also been blamed as one cause for a fall in R&D activity. The Japanese Ministry of Health, Labour and Welfare has pointed out that “to harmonise the

¹⁶⁶ Ministry of Health, Labour and Welfare of Japan (2002), pp. 38-39.

¹⁶⁷ Chapman (2003).

achievement of global competitiveness in the pharmaceutical industry with the drug pricing system, consideration from the medium-to-long term perspective is required, not simply of drug prices but also of drug benefits overall”.¹⁶⁸

By taking the long-term effects on the incentives to innovate into account more explicitly when determining price and reimbursement levels for new products, Europe’s position might be strengthened vis-à-vis the US. This is clearly an area where Member States may collectively wish to reward innovation but individually act to reduce prices and thus the pressure of healthcare on national budgets. The EC therefore has a role monitoring returns to innovation in Europe and facilitating co-ordination.

Recommendation No. 5: Call for more flexible pricing needs to take into account existing policy regarding the extension of market protection

There appears to be a growing recognition in Europe that in order to create an environment more conducive to innovation in pharmaceuticals, more flexible pricing structures would be required. This was a common theme raised by the participants of the CRA roundtable, both industry experts and regulators. All shared a belief that innovation should be priced in accordance with its value and that prices should be allowed to increase if additional trials prove additional value. Currently, however, there is generally no real possibility for manufacturers to receive a price increase for a product that is already on the market. The opportunity to achieve such a price premium could encourage further research and development after the product is launched. In fact, the Japanese Ministry of Health, Labour and Welfare has addressed issues of “optimisation of prices of original products” and “improved evaluation of breakthrough new drugs etc. through increase in rates of the corrective premiums” in the course of a drug pricing reform in 2002.¹⁶⁹

Although the possibility to receive price premiums in response to incremental innovation may increase the incentives to innovate, there are other possibilities to achieve the same aim. The recent review of the European pharmaceutical legislation has introduced the possible extension of the usual ten-year data exclusivity period for products that receive a significant new indication.¹⁷⁰ By extending market exclusivity, this provision could increase the returns to innovation but there needs to be a clear understanding of the conditions under which such an extension would occur and all must understand that the possible benefits of this provision would be tempered by the decline in the duration of product lifecycles, a decline that is expected to accelerate as the pace of innovation increases. Hence, co-ordination is required between regulators at the European and Member State level such that enough flexibility is built into and retained in the system to provide appropriate incentives for innovation.

¹⁶⁸ Ministry of Health, Labour and Welfare of Japan (2002), pp. 41-42.

¹⁶⁹ Ministry of Health, Labour and Welfare of Japan (2002), p. 41.

¹⁷⁰ See Appendix II for a detailed description of the review of the European pharmaceutical legislation.

Recommendation No. 6: New evidence supports the effectiveness of R&D tax credits but co-ordination required to maximise benefits to Europe

The effectiveness of R&D tax credits has often been questioned by academics. It was argued that R&D was insensitive to tax credits and these largely influenced the location of R&D rather than the level of R&D. More recent academic work has suggested R&D tax credits do work in terms of encouraging R&D and can be a useful tool for encouraging innovation.¹⁷¹

A number of countries are using or investigating the use of targeted R&D tax credits to encourage investment in certain therapeutic categories deemed to be in need of investment. A recent example is the UK Government's proposals for an R&D scheme related to vaccines research with the intention of providing an "even greater incentive to undertake R&D into the killer diseases of the developing world".¹⁷² There is a danger that tax credits are used to encourage the location among European Member States rather than in Europe as opposed to elsewhere. This will reduce the benefits from the European perspective. There is an argument that co-ordination of tax credits is required at the European level if the spill-over effects are to be fully taken into account. This means greater co-ordination between Member States in terms of the structure and therapeutic area where tax credits are proposed.

Recommendation No. 7: Improved public-private co-operation in research needed in Europe

Clearly, fragmentation of the research system impedes communication of research findings and slows the pace of innovation. This applies not only to communication across national borders, which might be relevant for the European Union, but also to communication between basic research undertaken in the universities and research institutions of Europe and that undertaken in the pharmaceutical industry.

In the US, the National Institutes of Health (NIH) is seen as fulfilling a crucial role in co-ordinating public and private research, bringing together funds, scientific knowledge and centres of excellence.¹⁷³ Each year, the NIH invests approximately \$28 billion of public funds in medical research. More than 80% of the funds are awarded through competitive grants to over 212,000 researchers at more than 2,800 universities, medical schools and other research institutions both in the US and abroad; 10% of the NIH funds are allocated to the Institute's own scientists (almost 6,000, most of them working at the NIH headquarters in Maryland). To allocate funds, the NIH identifies research priorities using a variety of different procedures, including a competitive peer-review system to identify the most promising research opportunities.¹⁷⁴

¹⁷¹ Bloom, Griffith and Van Reenen (2002).

¹⁷² Regulatory Impact Assessment – Improvements to research and development tax credits.

¹⁷³ CRA roundtable in Appendix IV.

¹⁷⁴ National Institutes of Health (2004).

At the European level, virtual institutes of health have been suggested to overcome the fragmentation of the research market.¹⁷⁵ In addition, the database on clinical trials that will be set up by the European Commission may lead to better communication among both public and private researchers.¹⁷⁶ Therefore, this problem has been identified, the suggestions need to be implemented and given appropriate funding.

11.2.3 LOW PRIORITY

Based on our findings in Phase I and Phase II, we consider the recommendations discussed in the previous sections as the most important ones in order to promote innovation in the pharmaceutical industry. In addition to these priority policies, there are other recommendations that we believe may promote innovative activity, but the effects of which are more difficult to achieve and potentially ambiguous. These recommendations relate to a single EU wide price, encouraging therapeutic reference pricing, facilitating greater public-private co-operation, monitoring cost effectiveness studies and improving access to venture capital.

Recommendation No. 8: Fundamental changes to reimbursement systems resulting in European prices unlikely to encourage innovation

Clearly, the increasing spending on health care is putting pressure on the government budgets in all European countries. Cost-containment measures and their likely effect on the incentives to innovate are described in Section 8 of this report. To the extent that cost containment measures and lower reimbursement levels for branded products reduce the returns to innovation, they will lead to lower incentives for pharmaceutical companies to invest in R&D. In addition, different prices in different Member States result in parallel trade of branded products, further reducing the returns to innovation, but – because the difference in margins often seems to accrue to the benefit of parallel traders and not consumers¹⁷⁷ – this has not led to significant savings for society.

Given that different price setting mechanisms also impede the realisation of the free internal market of the EU, the European Commission has launched a reflection process on alternative mechanisms to control health care spending, which explicitly includes the possibility of free price setting by pharmaceutical manufacturers. This could be complemented by national rebates or discounts negotiated with each Member State in order to ensure cost containment.¹⁷⁸

¹⁷⁵ High Level Group on Innovation and provision of medicines (2002), p. 18.

¹⁷⁶ European Commission (2003), p. 20.

¹⁷⁷ Whether parallel imports lead to lower prices for consumer is an area of intense debate. See Kavanos (2003) for a report finding that there are few benefits for patients. Ganslandt and Maskus (2004) reach the opposite conclusion.

¹⁷⁸ European Commission (2003), p. 15.

In theory, a system of uniform European prices set by the manufacturer could speed up the process of bringing a product to the market by avoiding lengthy negotiations with regulators and health care agencies. Yet, it seems that the main motivation of the European Commissions reflection process relates to the integration of the European market. Although a system of free and relatively uniform price setting might reduce leakage of profit through parallel imports, it does not in itself change the returns to innovation if the possibility of national discounts and rebates remains. There is the risk that negotiation over price will simply become negotiation over discounts and that nothing will change. Hence, there would be no improvement with regard to the speeding up of the reimbursement and price setting process. This proposal does not therefore appear a high priority for encouraging innovative activity unless it can be coupled with an initiative to increase pricing flexibility for innovative products.

Recommendation No. 9: Maintain vigilance over competitive effects of mergers

According to our findings from phase II, evidence to date does not support any loss in long-term innovative productivity resulting from the wave of mergers and acquisition during the 1990s. Indeed, there are signs that the causal relationship may have been the opposite and that merger activity may have been driven by the perceived reduction in new product opportunities and the need to fill product pipelines.

At the CRA roundtable, the effect of mergers on innovation was discussed extensively. The general conclusion, supported by the data, was that although mergers may lead to a period of disruption in the short term, the overall impact of past mergers on R&D was often positive. For example, by allowing a paradigm shift with regard to the organisation of R&D activities, mergers may lead to new structures for R&D departments that allow them to work more efficiently and increase their productivity. Overall, re-organised R&D appears to have been a beneficial effect of past pharmaceutical mergers.

Despite all the positive effects that mergers may have on R&D and innovation, continued vigilance of competition authorities is required in order to ensure that future mergers and acquisitions will not lead to a reduction in innovative activities. Therefore, we do not identify particular areas for merger policy. In contrast, there are concerns with the way that licensing agreements will be monitored in Europe and this remains an area where further consideration is required. In particular, the new Technology Transfer Block Exemption (TTBER) and Guidelines recently published by the EC potentially lowers the incentives to innovate.

Recommendation No. 10: Impact of therapeutic reference pricing on innovation needs to be understood

Therapeutic reference pricing was discussed in Section 8.3 of this report. As explained, the effect of therapeutic referencing pricing on the incentives to innovate depends on how

therapeutic groups are constructed and at what level reference prices are set. In theory, the effect can be either to increase or to reduce the incentives to innovate. Therefore, it is crucial that – when setting up therapeutic reference pricing – the likely effect on innovation is taken into account. Yet, to our knowledge there is relatively little published analysis regarding the impact therapeutic reference pricing has on the incentives to innovate in any of the countries where this has been recently introduced or where there are plans to do so soon (e.g. the Netherlands, Italy and Germany).¹⁷⁹ Instead, the focus of attention has been on encouraging substitutability and competition. An analysis of the impact on innovation would need to consider the how the structure of the therapeutic reference pricing system changed incentives to invest in R&D, in particular the effect of the:

- rules determining the therapeutic group;
- prices prior to a new group being established;
- differential impact on 1st, 2nd and 3rd movers and the speed of development.

Given that therapeutic reference pricing is relatively new in Europe but it could have significant ramifications for the incentives to innovate, we have found surprisingly little analysis of this. Hence, we believe that any European wide conclusions regarding the impact of therapeutic reference pricing on innovation should wait until lessons can be drawn from the experience in countries that have recently introduced or will soon introduce such systems; this is an area in which the EC should conduct further research.

Recommendation No. 11: European comparison of cost-effectiveness studies less important than how cost effectiveness interacts with pricing

The G10 recommendations called for the general development of health technology assessments with regard to clinical and cost effectiveness in the EU and in the Member States.¹⁸⁰ In response to the G10 process, the European Commission will provide a forum for information exchange and reflection on these issues and Member States have set up a working group to ultimately develop a common methodology for the assessment of relative effectiveness.¹⁸¹

If realised at the European level, a common methodology for the assessment of clinical and cost effectiveness of new medicinal products will provide a useful benchmark for assessing the on-going quality of innovation. However, the impact on innovation will depend on the connection of this assessment methodology with the reimbursement system. If premiums for innovative products are allowed, it can improve innovation, similar to the possible effect of

¹⁷⁹ One of the few papers to consider the impact of therapeutic reference pricing on the availability of new products is Danzon (2003).

¹⁸⁰ High Level Group on innovation and provision of medicines (2002), p. 17.

¹⁸¹ European Commission (2003), p. 11.

therapeutic reference pricing. If no premiums for highly cost and/or clinically effective products are possible, the effect on the incentives to innovate is unclear. Europe can fulfil a role monitoring the premium related to cost-effectiveness results and communicating how this varies around the Member States. As different Member States are still in the process of developing their policies on cost effectiveness, this is necessarily low priority.

Recommendation No. 12: Improving access to venture capital in Europe would be beneficial but difficult problem to address

Pharmaceutical innovation is a long-term risky investment. The lack of a European venture capital base, especially compared to the US, has long been identified as a problem. The industry experts at the CRA roundtable attributed the minor role that venture capital plays in the European pharmaceutical industry to three main reasons:

- Venture capital companies are usually interested in receiving returns within a time horizon of two to three years, which is not in line with the time periods appropriate for pharmaceutical development;
- There is no public co-financing in Europe similar to the way that the NIH effectively complements venture capital funds in the US; and
- Owners of small pharmaceutical companies in Europe are often reluctant to cede control to venture capital firms.

However, there is no evidence that the first and third of these differ substantially between the US and Europe. Instead, the role played by the NIH (through jointly providing finance with the private sector) in the US is suggested as offering a model to develop this on a European basis. While virtual centres of excellence may enhance the transfer of research information, complementing this by public funds might make the industry less risky and more attractive for private venture capital. However, given the scepticism of both industry and regulators regarding the prospect of encouraging a step change in the level of venture capital in Europe this should be seen as a low priority over the next five years.

11.3 Conclusions

There are already many plans to encourage innovation globally, within the European Union, and at the level of Member States. However, there is a clear danger in focusing on so many policy areas that efforts are too diffuse and lack of co-ordination prevents the true benefits from materialising.

In this report we have attempted to relate the size of the problem, the underlying causes and how these remedies meet up to the task at hand. We have identified seven recommendations where the European Commission, Member States and the industry should work together to improve the European environment for innovation:

- Focusing on how technical advances can improve the later stages of the development process (similar to the Critical Path debate in the US);
- Improved communication between regulator and industry during key phases of development;
- Addressing fundamentals to prevent future bottlenecks and increase industry capacity;
- Using branded prices to sustain incentives to innovate in the face of greater generic competition;
- Greater flexibility in pricing to reflect innovation in existing products;
- Co-ordinating R&D tax credits to maximise benefits to Europe; and
- Facilitating improved public-private co-operation in research in Europe.

These changes are necessary if Europe is to compete with the US and Japan as a location for innovative activity. These will also contribute to the global efforts needed to improve innovative productivity.

Appendix I: Types of applications and authorisations considered

We considered a range of issues to determine the most appropriate measure of innovation:

New indications – By focusing on new active substances, we do not capture innovations in terms of new indications for known active substances. Although new indications can be true innovations there are problems associated with using indications as a measure for innovative activity. First, it is difficult to identify those applications for marketing authorisations that involve *significant* new indications from the database.¹⁸² There is considerable debate whether it is possible to identify therapeutic value of a new indication at the stage of approval (see discussion on therapeutic advancement below). Second, there are only a few *significant* new indications each year (according to a representative of the Mutual Recognition Facilitation Group).

Part A and Part B products - We considered, as an alternative approach, to identify applications for marketing authorisations for "Part A and Part B products", which one could consider as a proxy for innovative products. Part A products are those that have to be filed with the EMEA and for which data are available. Part B products can either be filed centrally with the EMEA or can get authorisation through the mutual recognition procedure. However, the database of the Mutual Recognition Facilitation Group does not allow easy identification of Part B products.¹⁸³

Products vs. procedures/substances – The EMEA database on the centralised procedure marketing authorisations and the MRFG database for the mutual recognition procedure contain applications for new products, which may not involve new active substances. In the MRFG database new active substances lead to new "procedures". Each procedure may concern several "products". Products would, for example, also cover line extensions of existing applications to new strengths. Hence we decided to focus on procedures, which are started for new active substances, and ignore the number of products, which may not be innovative but reflect the development of the range by the marketing authorisation holder for a particular substance. We screened the database of the EMEA in a similar way. Finally, new applications for products are sometimes due to new brand names or applications for known substances by new marketing authorisation holders. By focusing on substances rather than products these applications are excluded.

¹⁸² The discovery of new indications could lead to variations or extensions of existing applications. Variations are changes to marketing authorisations that do not fundamentally alter the terms of the authorisation. Extensions do fundamentally alter the terms of the marketing authorisation and require a new application. This application may result in a modification of the existing marketing authorisation or in a new marketing authorisation.

¹⁸³ Based on communication with the MRFG.

Therapeutic advancement – As discussed in the section on the definition of innovation (Section 2.2) one would ideally like to measure the therapeutic advancement of an application for a new marketing authorisation. The FDA and some European authorities use categories for the expected therapeutic advancement of an application. Currently, no such measure exists on a European level.¹⁸⁴ We therefore considered the use of WHO ATC codes or other classification systems. This would require a presumption that those products that lead to a new ATC would be more innovative than those that do not. There are two main disadvantages attached to this:

- First, a final decision on the allocation of an ATC code is often taken only with significant delay.
- Second, the WHO states clearly that the use of the ATC codes as therapeutic classification system is limited: *“It is important to emphasise that the ATC classification does not necessarily reflect the recommended therapeutic use in all respects. Therefore, the ATC system should not be used as a tool for marketing purposes concerning efficacy, mechanism of action or therapeutic profile in relation to other drugs. It should be emphasised that assignment to different ATC groups does not mean a difference in therapeutic effectiveness and assignment to the same ATC group does not indicate therapeutic equivalence”* and *“The ATC system is not strictly a therapeutic classification system... Substances classified in the same ATC 4th level cannot be considered pharmacotherapeutically equivalent since their mode of action, therapeutic effect, drug interactions and adverse drug reaction profile may differ”*¹⁸⁵

There exists a classification of therapeutic value of medicinal products in France.¹⁸⁶ For each medicinal product applying for inclusion in the list of reimbursable medicines in France, the Transparency Commission (Commission de la Transparence) prepares an opinion, including an assessment of medicinal, pharmaceutical, epidemiological and economical aspects of the product. In 1999, the evaluation system was fundamentally changed by a decree fixing the criteria of the medicinal service delivered (service médical rendu, SMR) which serves as the basis for determining the reimbursement of a specific product. In its work, the Commission de la Transparence also assesses the improvement in SMR of a specific product compared to other products available in the market for the same indication (amélioration du service médical rendu, ASMR). There are five possible levels of an improvement in the medicinal service delivered:

I. Major therapeutic progress;

¹⁸⁴ Initiatives by the EMEA to increase the information on the therapeutic value (the MINE database) have been stopped.

¹⁸⁵ <http://www.whooc.no/atcddd/>

¹⁸⁶ Sources: <http://agmed.sante.gouv.fr/htm/5/avisct/indact.htm> and Annual Report 2002 of the "Agence française de sécurité sanitaire des produits de santé" (Afssaps), p. 95 (<http://agmed.sante.gouv.fr/pdf/5/rapt02nb.pdf>) and Presentation of the Commission de la Transparence (<http://agmed.sante.gouv.fr/pdf/1/colok43.pdf>).

- II. Important improvement in terms of therapeutic effectiveness and/or the reduction of undesired side effects;
- III. Moderate improvement in terms of therapeutic effectiveness and/or the reduction of undesired side effects;
- IV. Minor improvement in terms of acceptability, convenience to use and compliance; and
- V. No improvement.

For the purpose of this study, level I and also level II seem like the most appropriate ones to identify innovative products. The website of the French Health Products Safety Agency lists all opinions adopted by the Commission de la Transparence since 2001 (apparently the Commission started publishing its opinions online only in September 2001).¹⁸⁷ Unfortunately, in order to identify the products with level I or II of ASMR, one would have to check the available file for each product separately as the overview website only lists the product name, substance, the name of the company and the date of the Transparency Commission decision.

Double counting - In order to get a precise measure of the number of applications for marketing authorisations for medicinal products that contain new active substances we used application data from the mutual recognition procedure and from the EMEA. In order to avoid double counting and in order to focus purely on those products that are intended to be marketed in several Member States, we eliminated all "referred applications" from the EMEA database. Moreover, we eliminated all "repeat applications" from the MRFG database, i.e. those applications that refer to the same authorisation (e.g. to cover new Member States not involved in the first procedure).

Pre 1998 data - In terms of the time period covered, we used the period from 1998 to 2003. After 1995, when the EMEA was set up, there was a transition from national procedures to mutual recognition procedures. From 1998 all applications in a second European Member state lead to either a mutual recognition procedure or a centralised procedure. Thus, the application data from 1998 onwards is consistent.

¹⁸⁷ <http://agmed.sante.gouv.fr/htm/5/avisct/indact.htm>

Appendix II: Regulatory framework of the pharmaceutical industry

In this appendix we review recent changes in policy regarding intellectual property and the review of European pharmaceutical legislation.

Intellectual property and general competition policy rules

All developed countries that have exhibited high rates of invention and investment leading to new products have strong IP laws. Investors in innovative technologies such as venture capitalists want IP protection when making investments in the development of these innovative technologies. Clearly, the protection of intellectual property is a key issue for innovative activities. The value of the intellectual property and the incentives to innovate will not only be affected by patenting regulation but also by general competition policy rules, which may lead to mandatory licensing or affect the M&A activity in the industry.

Intellectual Property and Competition Policy

Uncertainties regarding intellectual property protections increased the risk associated with innovation investments. After all, there is little motivation to invest when the dividends might be given away. In recent history, several factors have caused manufacturers to question the intellectual protections their therapies enjoy. First, there have been a series of litigation cases that address appropriate pricing and marketing practices for pharmaceuticals, including methods to compete against the entry of generic competitors. Second, global trade negotiations contributed to uncertainty regarding intellectual property rights. For example, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) accord, which came into effect in January 1996, provided contradictory intellectual property signals to manufacturers. TRIPS provided relief from illegal violation of patent rights but also allowed countries to take compulsory licenses from manufacturers.

Patent criteria for biological products are relatively new and untested. Patents have issued for a number of genes, proteins, and pathways despite the dearth of commercialised therapies. The proliferation of patents threatens to generate “patent thickets” where manufacturer patents mutually block development.

Licensing

The pharmaceutical industry is characterised by high specific investment in R&D and comparatively low marginal costs. Like most industries with these characteristics, the pharmaceutical industry can be characterised by a significant degree of concentration

(depending on therapeutic area), a large amount of price discrimination (in order to try to recover the “sunk costs” incurred in R&D), and to exhibit high profit margins. Competition authorities tend to be concerned by all three issues. Thus, the competition authorities’ regulatory approaches have traditionally been important for the incentives to innovate in the pharmaceutical industry.

One relevant change of legislation is the new Technology Transfer Block Exemption (TTBER) and Guidelines recently published by the EC. The TTBER represents a distinct departure both in form and substance from the previous TTBER. The new TTBER trades off the long run effects of weakening IP incentives against the short-run benefits of increased competition. Thus, the Commission asks two questions:

1. “Does the agreement restrict actual or potential competition that would have existed had no licence been granted?” (Para.14a)
2. “Does the agreement restrict competition that would have existed in the absence of its alleged restriction(s) of competition? This question relates to the issue of whether or not the restriction is objectively necessary for the conclusion of the agreement.” (Para.14.b)

At paragraph 16 the Commission states that

“The pro-competitive effects of licence agreements must be balanced against the restrictive effects in the context of Article 81(3). When all four conditions of Article 81(3) are fulfilled, the restrictive licence agreement in question is valid and enforceable”.

Standard approach to IP is that licences should be able to convey the full monopoly rights granted by IP law and licences should not restrict competition beyond what was granted by IP law. This is captured by asking the question: does a licence eliminate competition that would otherwise have existed?

Thus, some commentators (Lind and Muysert 2003)¹⁸⁸ suggested that the Commission’s approach is a radical departure from standard practice, which will:

- Reduce the value of IP and hence the incentive to innovate;
- Lead to companies changing their business decisions in order to avoid licensing IP (e.g. integrating vertically, not exploiting the IP in some jurisdictions).

¹⁸⁸ Most of the criticism related to the draft TTBER also applies to the adopted TTBER. See also CRA 2003.

Patents

There has been a long debate about whether stronger or weaker IP laws would be preferable in promoting innovation and growth.

There have been no major changes in IP legislation in the past and none are foreseen for the immediate future. Note however that the pharmaceutical review legislation, which we discuss in more detail below, will lead to changes in (and – viewed at the EU level – effectively a strengthening of) the data protection system.

Pharmaceutical review legislation

The EU legislation with regard to pharmaceuticals has recently undergone a review process, as required by the original regulation setting up the EMEA in 1995. The main results of the review process are the “Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use” and “Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency”¹⁸⁹. In addition to the two pieces of official review legislation, there have been other legislative changes over the last couples of years, including the Clinical Trials Directive¹⁹⁰ and a Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissue and cells.¹⁹¹ Moreover, the European Commission has started another consultation period for its proposal on encouraging research and marketing of paediatric uses of medicines.¹⁹² This section presents the main changes brought about by the pieces of legislation mentioned above. In particular, the likely effect on innovation in the European pharmaceutical industry is analysed.

Review legislation

As explained, the review of the EU pharmaceutical legislation consists of two legislative pieces, a directive amending Directive 2001/83/EC on the Community code relating to medicinal products for human use and a regulation laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation Medicines Agency.

¹⁸⁹ Both pieces of legislation are available at <http://pharmacos.eudra.org/F2/review/index.htm>.

¹⁹⁰ European Parliament and Council (2001).

¹⁹¹ The amended Commission proposal for this directive is available at http://europa.eu.int/eur-lex/en/com/pdf/2003/com2003_0340en01.pdf

¹⁹² European Commission (2004).

The new Directive was passed by the European Parliament on 17 December 2003, adopted by the Council on 11 March 2004 and will enter into force in 2005. The new Regulation will replace Council Regulation No. 2309/93 that laid down the Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and that established the EMEA. Given the significant overlap between the two documents, we describe and analyse them jointly in the following section:

- ***Data protection and exclusivity period.*** The review legislation harmonises the exclusivity and protection period for data resulting from pharmaceutical and pre-clinical trials and the assessment of a product's safety and efficacy that must be submitted when applying for marketing authorisation. Currently the data exclusivity period is 10 years for products that received marketing authorisation through the centralised procedure and at least 6 years for products going through mutual recognition (variations depend on national legislation in the Member States). As of 2005, data exclusivity will be guaranteed for ten years for all products, regardless of the authorisation route taken. The ten-year period starts at the granting of marketing authorisation and is split into a data protection period of eight years and two years of data exclusivity. For a significant new indication, an additional year of data exclusivity can be granted (this is why the new provision is also called 8+2+1 rule). The new rule ensures that generics can only enter the market ten years after the reference product, but can start research and development work in the EU already two years before the data exclusivity of the reference product expires (the so-called Bolar provision). For significant OTC switches (i.e. when a prescription medicine is re-classified as a non-prescription drug) and for new uses for well-established medicines, a one-year data protection period can be granted, which is intended to increase the incentive to conduct further research on already existing and marketed products. The new data protection periods will only apply to applications submitted after the new legislation comes into force. There may be room for derogations from these periods in some cases, e.g. in the new Member States that usually have shorter periods of data protection.
- ***Extension of the centralised procedure.*** With a view to harmonising the internal market for new medicinal products, the centralised procedure becomes compulsory for products in four new therapy areas (AIDS, cancer, diabetes and neurodegenerative diseases). Annex I of the regulation, which lays down for which products the centralised procedure is mandatory, can be modified after four years and, according to the press, it is planned to extend the centralised procedure after these four years to two more therapeutic categories (autoimmune and viral diseases).¹⁹³
- ***New definitions.*** New definitions of generics and bio similar products are intended to provide greater clarity on which products fall under EU pharmaceutical legislation (e.g. as opposed to food supplements etc.).
- ***Structural changes to the EMEA in light of EU enlargement.*** The EMEA's name will be changed to European Medicines Agency and it will comprise a Committee for Medicinal Products for Human Use, a Committee for Medicinal Products for Veterinary Use, a Committee on Orphan Medicinal Products, a Committee on Herbal

¹⁹³ Based on *Scrip*, 10 March 2004.

Medicines Products.¹⁹⁴ The structural changes are intended to focus the Agency's work more on innovation and to reinforce its scientific profile (increased scientific and regulatory advice to industry). E.g., all committees mentioned above are required to establish a standing working party with the sole task of providing scientific advice to undertakings.

The regulatory procedures will be rationalised and simplified to improve the transparency of decision-making and accelerate the availability of new products. The new Committee for Medicinal Products for Human Use will be responsible for formulating the opinion of the Agency on any matter concerning the admissibility of the files submitted in accordance with the centralised procedure, the granting, variation, suspension or revocation of an authorisation to place a medicinal product for human use on the market. The legislation requires the new Agency to make publicly available all regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products that is non-confidential.

Supervision and pharmacovigilance will be strengthened. For example, the Commission receives the right to initiate inspections of marketing authorisation holders, manufacturers or importers; marketing holders must have "permanently and continuously" at their disposal a qualified person responsible for pharmacovigilance, including the establishment and management of an information system concerning all suspected adverse reactions that can be accessed at a single point within the Community; the Commission shall draw up a guide on the collection, verification and presentation of adverse reaction reports; cooperation between the Agency and the WHO as well as among Member States shall be increased.

- ***Supply chain issues.*** Marketing authorisation holders and distributors of a medicinal product in a given country are now responsible for ensuring appropriate and continued supplies of the product so that the needs of patients in the concerned Member States are covered.
- ***Evaluation of therapeutic value.*** While the importance of an assessment of the comparative efficacy of new products with regard to products that already exist in the same therapeutic class and of the added therapeutic value of new products is acknowledged, the review legislation provides that this evaluation should not be conducted in the context of the marketing authorisation process.
- ***Support of SMEs.*** The legislation includes provisions for reduced or deferred fees and administrative assistance for SMEs marketing medicinal products that are authorised through the centralised procedure.
- ***Ethical requirements in clinical trials.*** Directive 2001/20/EC provides for ethical requirements in relation to clinical trials ("good clinical practice in the conduct of

¹⁹⁴ Moreover, the Agency will consist of a Secretariat providing technical, scientific and administrative support for the committees and ensuring coordination among them, an Executive Director as its legal representative and the manager of its day-to-day administration and a Management Board consisting of one representative per Member State and representatives of the European Commission.

clinical trials on medicinal products for human use”). These requirements apply to all medicinal products authorised within the Community. For products that are destined for authorisation in the Community but for which clinical trials were conducted outside the EU, it should be verified at the time of evaluation of the application that these trials were conducted respecting the principles of good clinical practice and the ethical requirements called for in the Directive set out above.

Commission's proposal on encouraging research and marketing of paediatric uses of medicines¹⁹⁵

The Commission proposes a system of obligations and incentives/rewards in order to stimulate the development of medicinal products that meet the therapeutic needs of paediatric patients. The Commission's proposal has been influenced by the European experience with orphan drugs and the US experience with the promotion of paediatric products.

- ***New products and products already authorised and covered by a patent or a supplementary protection certificate.*** The Commission proposes a requirement to present the result of studies in children according to an agreed paediatric investigation plan at the time of marketing authorisation application or application for a new indication, new dosage form or new route of administration. A waiver system will ensure that research in children is only conducted to meet the therapeutic needs of children. The requirement for data in children will not block or delay the authorisation of medicines for other populations, through the use of deferrals from the requirement for data in children. The submission of data in children – irrespective of the result – and the updating of the product information should be linked to the reward of a six-month extension of the supplementary protection certificate (this is a type of patent extension harmonised across the EU).
- ***Products not covered by a patent or supplementary protection certificate.*** Given that these products are no longer patent protected, requirements at the time of application and the extension of data exclusivity will not be effective incentives to promote paediatric studies. For these products, the Commission proposes the incentive of additional data protection on any new studies on the safety, quality and efficacy of the product in children linked to a new type of marketing authorisation (Paediatric Use Marketing Authorisation, PUMA) together with a study programme to fund or part fund research into the paediatric use of off-patent medicines (Medicines Investigation for the Children of Europe, MICE). It is hoped that this will provide an incentive for companies to invest in paediatric research for old products.

Other measures are planned in the following fields:

- ***Infrastructure***, e.g. set up of an expert committee, the Paediatric Board (PB), at the EMEA and definition of procedures regarding paediatric investigation plans and marketing authorisations.

¹⁹⁵ Based on European Commission (2004).

- **Knowledge sharing**, e.g. free scientific advice from the EMEA to companies, survey of the use of medicines in children in the EU, inventory of the therapeutic needs of children.
- **Transparency**, e.g. database of agreed paediatric transparency investigation plans and studies conducted as a result of them, requirement for the industry to submit to competent authorities pre-existing studies relating to the use of medicines in children and published annual reports on the companies that have benefited or failed to comply with the measures in the paediatric legislation.
- **Pharmacovigilance** requirements above the requirements for other non-paediatric medicinal products, e.g. the requirement to outline the pharmacovigilance plans as part of the application for marketing authorisation and the authority for regulators to require a risk management system or post-authorisation data collection if a particular product is associated with a safety concern.
- **Market access measures**, e.g. access to the centralised procedure for applications that contain the results of studies following from an agreed paediatric investigation plan, use of the community referral procedure to obtain a Commission decision on paediatric use for nationally authorised products and a requirement for authorised products that were newly granted a paediatric indication to market the product, taking into account the new indication, within a set period.

Non-review legislation¹⁹⁶

- **Directive on human tissue and cells.** The directive was adopted by the European Parliament in March 2004. It sets standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells. The Directive leaves it up to the Member States to implement their own rules on human cloning and other issues. The aim of the Directive was to further the opportunities offered by tissue and cell therapy without causing unacceptable risks for donors and recipients.
- The **Clinical trials Directive** (2001/20/EC) must be implemented in national law by 30 April 2004. The Directive sets minimum standards with respect to clinical trials in general, clinical trials on minors and on incapacitated adults that are not able to give informed legal consent. Member States are required to take measures that are necessary for establishing and operating Ethics Committees that shall give their opinion on any issue requested prior to the commencement of a clinical trial. In addition, a European database bringing together information on the content, commencement and termination of all clinical trials carried out in the Community will be established.

¹⁹⁶ Based on *Scrip*, 10 March 2004.

Other issues¹⁹⁷

- In the context of the G10 recommendations, the Commission raised the prospect of allowing pharmaceutical firms to set their own prices for new products within a narrow EU band and manufacturers making rebates to social security systems as appropriate.
- Setting up of the new European Centre for Disease Control in Sweden (along the lines of the US CDC). The Centre will have the following main tasks:

Epidemiological surveillance and networking of laboratories;

Technical operation of an Early Warning and Response System (EWRS);

Scientific opinions in the area of communicable diseases;

Technical Assistance and Communication in the area of communicable diseases.¹⁹⁸

¹⁹⁷ Based on Scrip, 10 March 2004.

¹⁹⁸ http://europa.eu.int/comm/health/ph_overview/strategy/ecdc/main_task_ecdc_en.htm

Appendix III: Causal factors for the fall in marketing authorisation applications identified by the FDA and the EMEA

The FDA lists the following factors contributing to the decline in new product applications:¹⁹⁹

- The past investment climate. With total development time averaging about ten years, today's applications are the result of R&D that began a decade ago. Industry data show that in the early nineties, the growth rate in R&D investments dropped to the lowest level in 20 years. This dip may be having an impact now.
- Industry analysts have cited the difficulty of capitalising on the vast quantities of genetic, genomic and proteomic data now becoming available. Some analysts think that this 'deluge' of data has actually caused a reduction in R&D productivity, as the industry shifts from traditional chemistry to cutting edge biotechnology.
- The FDA has observed that mergers within the industry may be causing an elimination of candidate drugs that are within the same class. This phenomenon would decrease the number of "me-too" drugs submitted.
- European regulators, facing a similar trend, have cited recent mergers as a factor: merged entities select only the most promising prospective "blockbusters" for further development. The net result of a corporate merger on the size of the company's product pipeline is described as "Twenty plus twenty equals twenty".
- The managed care environment is also decreasing the incentive to develop numerous "me-too" drugs when several members of a class have been approved. This also can be seen once the first generic within a class is approved.
- Some have suggested that the FDA has increased study requirements and the increased cost and time delays have contributed to a slowdown in applications. Scientific advances over the past several years have enabled earlier detection of life-threatening cardiac risks and drug interactions; these advances have protected patients from harm. Earlier discovery of these problems enables companies to shift resources to other candidates, but may also have resulted in a temporary slowdown in submissions.
- Many of the "easy targets" for drug development have already been utilized. Some industry analysts have noted that the pharmaceutical R&D focus has shifted to develop drugs for chronic and more complex diseases with large market potential. These conditions, however, often involve much larger patient populations and/or longer-term studies that require more expensive trials to document safety and efficacy. Some cite an "increased FDA conservatism" triggered by recent drug withdrawals. The current withdrawal rate for NMEs approved under PDUFA (2.5%) is not higher than the pre-PDUFA rate (2.7%). There is no evidence of an excess rate of withdrawals in recent years. Furthermore, an analysis of the percentage of first-

¹⁹⁹ FDA (2004).

cycle approvals for priority NMEs over the 10 years of PDUFA does not show any evidence of a systematic change in the likelihood that a priority NME application will be approved on the first cycle. With regard to standard NMEs, there may be a slight trend toward decreased first-cycle approvals in the last several years of PDUFA II, however, it is difficult to ascribe this observation to an FDA “conservatism” given the concurrent shortening of the PDUFA review clock for standard NDAs from 12 to 10 months during this time period.

EMEA roundtable

On 6 June 2003, the EMEA held a roundtable on “The Shortfall of Marketing Authorisation Applications”. Participants included the European Commission, National Competent Authorities, the FDA, representatives of the pharmaceutical industry, EFPIA and EuropaBio. There were introductory presentations from CMR, TUFTS and the ABPI.

These presentations identified that the decline in marketing authorisation applications was due to:

- A real reduction in new chemical substances (NASs);
- Fewer multiple applications; and
- Delays in plans of pharmaceutical companies.

The roundtable attempted to understand the causal factors and identified the following:

- Strategic choices made by industry in 1990s had not led to the increase in new products that had been predicted. The strategic choices included mergers and acquisitions, optimising returns from existing products, focusing on blockbusters, and an increase in the duration and costs of R&D;
- Tightening of resources for reimbursement of R&D. In particular, the reduced prices in Europe, and expenditure containment through the Medicare programme in the US;
- The 4th hurdle, i.e. demands for cost effectiveness and benchmarking against comparators leading to increased clinical trials and pharmaco-economic analysis;

The role played by regulators was seen as positive, but there was some concern regarding the increased demand for clinical trials.

Appendix IV: Summary of the CRA roundtable with industry experts and regulators

This appendix presents the summary of a roundtable with industry experts and representatives of regulatory bodies organised by CRA as part of this study.

Purpose of the roundtable

As part of CRA's assignment to investigate whether there is an innovation crisis in the pharmaceutical industry, a roundtable was held on the 25th of June 2004 at the CRA's office in London, with representatives of the industry and regulators.

The roundtable was an informal one-day workshop, which had as its aim to get feedback on the results of phase I of the CRA project (identifying whether there is a crisis in innovation) and a subsequent discussion about the underlying causal factors and potential remedies. The roundtable was intended to focus on the industry perspective and issues at the European vs. US level. Discussions with European national regulators had been achieved through other means. The rules of the day were the following:

- Views were taken to be those of the individual rather than the organisation they represented;
- No quotes would be attributed directly;
- The discussion and conclusions from the roundtable would be circulated for comments. A revised and updated summary of the roundtable would form an annex to CRA's final report and would be sent separately to roundtable participants; and
- The notes would be shared with the organisations that had been invited, but were not able to attend the roundtable, in order to get as representative a view as possible.

We would like to thank all those who attended the roundtable and gave up so much of their time to assist with this project. We highly appreciated the spirit in which participants entered into the debate. In its organisation of the roundtable, CRA was greatly assisted by EFPIA, who co-ordinated attendance to ensure that members of EFPIA's R&D committee and EFPIA's Economic & Regulatory Affairs committee would be able to attend. In addition, the roundtable benefited considerably from the participation of the US Food and Drug Administration, to whom we would like to offer special thanks.

Is there a crisis in innovation?

The discussion on the phase I results focused on five areas:

- Are there particular problems regarding innovation in biologics in the EU?
- Has the probability of successfully developing a product and of a product moving from one development phase to the next changed substantially?
- What is a good measure of innovation for a pharmaceutical product, i.e. how do we measure quality?
- What is the fundamental reason for the drift of R&D to the US?
- Are patents a good measure of innovation?

Are there particular problems regarding innovation in biologics in the EU?

There is a clear concern that the EU is lagging behind the US in terms of the development of biologics. Appraising this lag in quantitative terms is complicated by changes in the definition of the data. For example, there is a review going on in the US with regard to moving some biologic products to the Centre of Drug Evaluation and Research (CDER) at the FDA. However, there appeared to be agreement among the roundtable participants that the US was stronger in biologics than Europe. Still, there was some debate regarding the underlying reason.

One proposed hypothesis was that small biologics require partnerships with large pharmaceutical firms and that the relationships between biologics and big pharma companies in the EU were not as strong as those in the US. This view was not held by the whole group, with a number of participants suggesting that this might simply reflect more US biologics companies, who would naturally favour teaming up with US big pharma in the US. As there are more biotech companies in the US this is inevitable. It was pointed out that for some companies it is a first priority to find a partner that can help to make the product a success in the US.

There was a strong belief that the fragmented European market made approving biologics (often from small companies) more problematic. Although there is a centralised procedure, in practice the EMEA committees work as groups of national experts, rather than a single team. This makes the European process “more of a lottery”. In contrast, in the US there is a single regulatory organisation and one set of relationships to develop. In Europe, small companies need to build relationships with many Member States, but without a large number of products in their portfolio this imposes a large cost on small companies. This problem is magnified in ‘new science’ as the identification of the key audience is more difficult and changes. In the US, the “Biologics Licence Application” (BLA) was set up to address this issue. There was a general point that in Europe there is less interaction with the regulator compared to the situation in the US.

There was agreement that compared to the US, there has long been a problem of too little venture capital in markets such as the UK. This was not a new issue and roundtable participants did not see it as an issue where progress could be made.

In the US, money from venture capital firms is complemented by funds from the National Institutes of Health (NIH) budget. The NIH allocates about \$28 billion of federal funds to basic research every year (due to the Bayh-Dole Act there is now a loss of federal funding, but there is an increased incentive to commercialise). Although much of the NIH funds are focused on basic research, they are also used to develop products. In some cases, states and regions form consortia to attract business.

Has the probability of successfully developing a product between Phases changed substantially?

There was some debate as to whether it was a reasonable or useful 'initial' assumption to assume constant probabilities of success from one phase to another in a model to develop a baseline forecast of the number of products being authorised over the next five years. There was concern that these probabilities might not stay constant:

- Companies become able to make better predictions regarding whether a product will be a success;
- 'Fail fast & fail early' might have become more important, possibly changing the probabilities; and
- Getting better tests in Phase I and Phase II will result in a better selection of attractive compounds to develop further.

There was a strong belief that improvements in innovation could be brought about by improving the process of drug development which might change these probabilities:

- The analysis of Janet Woodcock at the FDA and the critical path initiative suggest that there has been stagnation in development at least partially due to the fact that many of the 'tools' we are using are 30 years old; and
- New tests have been developed (bio-markers), but companies will only be willing to use them if they are accepted by regulators as companies might otherwise be told by the regulators that the test was not an appropriate end point.

In particular, new biomarkers have the potential to speed the availability of medicines to patients if they can also be used for regulatory decision-making. They are already used to inform development decisions in Industry (e.g. for early clinical 'proof of concept'). There is a progression and continuum from 'biomarker' (used as a development tool) to 'surrogate end-point' (sufficiently widely accepted to be used as the clinical basis of approval). Historically only a few biomarkers have gained acceptability as surrogate end points (e.g. blood pressure or cholesterol levels in cardiovascular medicine).

What is a good measure of innovation for a pharmaceutical product, i.e. how do we measure quality?

There was some concern with regard to putting too much weight on US data for the priority process as a measure of quality. The data prior to the Prescription Drug User Fee Act (PDUFA) were not operating under the same system and one might therefore not be comparing like with like.

There was considerable scepticism regarding whether a measure for 'quality' was possible and a concern that medicines that constitute incremental innovations are mis-described as 'me-too' drugs:

- The measures that regulators (in Europe usually the authorities responsible for making decisions on pricing and reimbursement) use to assess innovation might not be those that are most beneficial to patients, e.g. a new once-a-day formulation may be very valuable for a patient and result in better compliance;
- Every so-called me-too is to some extent different from other products (otherwise it would not get patented) and these small differences might prove to have substantial advantages for some patient sub-groups in real-life use;
- Too high hurdles for incremental innovation may lead to a reduction in innovation, e.g. atenolol may not have been launched. It is usually not the first, but the "nth" product in a certain market that becomes the blockbuster; and
- It is not really possible to know if the product is innovative until it is widely used.

The value put on products is also likely to vary considerably between countries/regions as the final outcome of an evaluation is not only dependent on the product and the data used but also on more variable factors such as priorities set, financial considerations, market situation, availability of alternatives etc.

Equally, some R&D areas might be socially valuable, but not perceived as important by society. Consequently, people might not be willing to pay much for prevention:

- There is little work done on antibiotics as these are only aimed at a small number of cases (after current treatment does not work); and
- Vaccines cannot be too expensive so as not to deter vaccination.

The overall conclusion was that measures such as fast track approvals were weak proxies for innovative quality, but that in general a measure of this kind would be extremely difficult if not impossible.

What is the fundamental reason for the drift of R&D to the US?

It was stated that there is more concern regarding innovation in the European theatre than a concern regarding the ownership of the companies.

There was an overall concern that although there are many positive aspects in the recent review of the European pharmaceutical legislation, there remains a concern that the EU regulatory system is not sufficiently joined up.

The general business environment was mentioned as an important factor for the choice of location, e.g. an educated labour force, tax breaks, but also factors that directly influence the environment for research, such as freedom to operate (e.g. stem cell research) and animal rights issues.

Are patents a good measure of innovation?

The number of patentable products that are being developed in Europe was proposed as a useful measure to see where new sciences will be based. However, it was also pointed out that it is difficult to infer value added by looking at patent data as there is an incentive to get a patent for a certain product in all markets. CRA were referred to the DTI innovation report²⁰⁰ as a useful analysis of these issues. It was also suggested to look at companies that are associated with patents.

Patent regulation was not seen as a significant impediment for innovation.

The bottleneck of Phase III development

One hypothesis that was generally supported around the table was that the apparent bottleneck of Phase III reflected the industry's limited capacity to undertake Phase III trials. This constraint was due to a combination of factors:

- Financial constraints;
- Human resources;
- Number of patients; and
- Limited number of doctors with expertise to be able to undertake complex trial programmes.

This means that at any one time it is only possible to have around 300 products in Phase III.

²⁰⁰ DTI (2003).

The expansion in Clinical Research Organisations (CRO) is addressing capacity issues and the expansion of research undertaken in EU Accession countries is resulting in more research for the companies' money. The industry was working to raise capacity where bottlenecks were identified.

There was a perception of a ratchet effect: Each big study implies that regulators will require future studies to be even bigger.

The group thought it would be interesting to look at failure rates for 'innovative products' (first-in-class) versus so called 'me-toos' (follow-on products) – CRA was referred to CMR who have recently looked into this.

It was also felt that it is too early to see the benefits of the kill-early strategy. However, it was also noted that an increase of products in phase I and II, but not in phase III is in line with more biologics and a higher attrition ratio.

The cost of innovation

The discussion on this topic focused on:

- Why did the costs of R&D increase so significantly?
- Could the regulator help reduce the costs of innovation through better communication?
- Is the Clinical Trials Directive good for European competitiveness?
- What is the impact of new technologies?

Why did the costs of R&D increase so significantly?

It is certainly the case that trials have become larger and more complex than they used to be (for example although new oncology products might be targeted at small groups, a new Cox II inhibitor requires about 20,000 patients). Discussing the relationship between complex therapies and growth rates, there was some surprise regarding the growth areas and whether they were the most expensive ones (CNS, anti-infectives). The inclusion of HIV in anti-infectives was thought to be responsible for this relationship. There was also a question as to what the cost included, for example, if they included the costs of all phases and whether the picture would be the same if we excluded Phase IV trials.

However, the roundtable participants were not surprised that costs are increasing and attributed this to:

- More concentration on chronic therapies; and

- Combination therapies and co-morbidities that have made regulators more risk averse, creating higher demands from regulatory authorities for safety and tolerability data.

However, there was a feeling that clinical trials are currently resulting in the collection of too much data, this might be cut by as much as 50%.

More thought needs to be put into finding the appropriate type of study for chronic therapies. In particular it was noted that there is likely to be less value in using a short-term study for a chronic therapy. New end points need to be used (looking beyond impact on mortality) and more emphasis should be placed on Phase IV trials.

At the end of the 1990s there was an epidemic of Phase III failures. Regulators are now more risk averse than they used to be. This represents a bigger challenge in the EU due to more groups that need to be co-ordinated.

There is a recognised trade-off between earlier access and the likelihood of finding problems with a product in phase IV. There was a question as to whether regulators were doing enough to clarify this trade-off:

- If access is granted earlier, what are the implications for on-going studies – it was not resolved whether this would represent a good thing or an increased burden for the industry;
- It is important that regulators make clear what is and what is not a regulatory failure. If a product fails – this is not a regulatory failure – this is inevitable to some extent; and
- This requires doctors and patients to be educated with regard to safety and risk issues.

The need to do comparative studies is also increasing the cost of trials. Each trial sets a precedent for competitor products coming into the market that need to show comparable results. In designing studies, industry is very careful to consider studies of existing/competing products. This leads to escalation in the amount spent on trials, even if the original studies were not undertaken with the aim of preventing entry of competitors.

Could the regulator help reduce the costs of innovation through better communication?

There are Phase II meetings between companies and the FDA in the US, but they are not undertaken in the same way in the European Union. The meetings require significant resources, but result in a formal understanding of the view of particular end-points and significantly reduce regulatory uncertainty.

In the EU there is a general concern regarding moving goal posts during the development process. A number of specific issues were also identified:

- One area to look at would be whether a more formal process at the end of Phase II would be useful in Europe.
- For small companies, a significant degree of “hand holding” by the regulator would be required which is not necessary for big pharma companies.
- In the US, the FDA has performance goals with regard to the interaction with industry during the development process.
- For this to work the regulator needs to have the right kind of expertise and the companies need to understand where this resides within the agency and how to interact with it.

Is the Clinical Trials Directive good for European competitiveness?

Overall, it was felt that the Clinical Trials Directive would not be good for European competitiveness. Problems were reported regarding the implementation of the new process. Implementing the Directive would be likely to reduce (or at least not improve) any advantage the EU currently has with regard to the cost of clinical development compared to the US.

The ability to undertake trials was seen as an advantage of the US, where companies feel that they are more likely to get the trial undertaken in the way required, i.e. there is a perceived quality advantage for the US.

What is the impact of new technologies?

There was an argument that the industry had overstated how fast new technologies could be turned into marketable products. While genomics/proteomics and new technologies are certainly very important, expectations on how quickly they would have an impact were far too high. Industry suffered from its own hype.

For example, new technologies have identified many targets but the industry needs time to work out how to assess these targets. High throughput screening is only a crude tool to use.

The overall conclusion was that that it is important to bring down the costs of product development to encourage more products to be brought forward into development. Regarding proposals to improve clinical trials, CRA was directed to a number of studies undertaken for the Pharmaceutical industry competitiveness taskforce.

The returns to innovation

The debate on the returns to innovation focused on:

- New product prices and the share of revenues associated to new products; and

- The dangers from therapeutic reference pricing and cost effectiveness studies.

There was general agreement that parallel imports continue to be a problem for big pharmaceutical companies with little corresponding benefits for payers. It was agreed that solving this would be beneficial but beyond the scope of the CRA assignment.

The share of new products

There was some debate regarding the share of resources devoted to older products. In particular, the discussion revolved around whether there is still risk aversion to the first product in a class and whether this was reasonable given the known safety of older products to sustain their remuneration.

Even if prices of new innovative products in the US and Europe are not so large, one needs to remember that in the US price increases are possible but that this is not the case in Europe. There is no flexibility to raise prices if phase IV trials show high effectiveness.

Therapeutic reference pricing and cost effectiveness

The costs of getting a product approved is one thing. Companies will also need to ensure that a newly launched product is positively received by payers. Increasingly this involves evaluation mechanisms, usually conducted prior to the reimbursement decision, aimed at identifying the added value and/or cost-effectiveness of a product. Product differentiation is key to ensure a positive outcome. While a positive outcome of added therapeutic value/cost effectiveness assessments may allow innovative products to have higher prices, there is not necessarily a causal link between the progressive availability of new evidence as the product is used in real-life practice and an upward readjustment of price level. All too often, evaluations are still intended purely as a cost-containment or access delay mechanism.

The nature of drug development is unpredictable. There is no guarantee that the first drug to market will be the best. Follow-up drugs compete on quality, as they often offer superior efficacy, dosing or safety profile.

Reference pricing, in particular therapeutic reference pricing, generally fails to reward innovative products. It is a blunt system that often does not properly assess differences between products. Better dialogue between a pharmaceutical manufacturer and national authorities must be encouraged and made possible by establishing appropriate mechanisms. This dialogue should allow more transparency and predictability and create a better understanding between industry and payers on the value that is given to the therapeutic progress achieved by a medicine.

Financing and industry restructuring

In this section we focused on the problems associated with venture capital and the impact of mergers on the innovative process.

Venture capital

Access to capital is a big issue for small pharmaceutical companies, but has not been an important issue for big pharma. Still, it has resulted in many relationships between big and small pharma. Access to venture capital is more difficult in Europe than in the US, which is mainly due to the following reasons:

- Venture capital companies are usually interested in receiving returns within a time horizon of two to three years, which is not in line with the time periods appropriate for pharma development;
- There is no public finance in Europe similar to the way that the NIH effectively complements venture capital funds in the US; and
- Owners of small pharma companies in Europe are often reluctant to give up control to venture capital firms.

The impact of M&A

There was general agreement that the justification of M&A had not solely focused on R&D productivity, but had also had to do with maintaining growth targets and the management of revenues and costs. However, mergers and acquisitions certainly led to the opportunity for process improvement in research.

Although it was accepted that in the short-term mergers lead to a period of disruption, the overall impact of past mergers was seen to be often positive.

The example of the GlaxoSmithKline merger was discussed, in particular the impact of the merger on the recognition that the R&D sector of GSK would be too large to manage and this would have to be run “as if it was a biotech”. This led to the creation of centres of excellence, which appear to be very successful in increasing the productivity of research. The restructuring had required considerable resources in change management and considerable commitment from senior management. Getting this focus was helped greatly by the fact that the merger allowed a paradigm shift in the way the company was organised.

Overall, re-organised R&D appears to be a beneficial effect of mergers. All research teams that left one pharma company soon relocated to others.

Summary and recommendations

Is there a crisis?

- There was agreement that the main factors of concern are the fall in R&D productivity and the move of R&D to the US;
- The probability of entering Phase III may be reduced (better tests in Phase I and II, better predictions regarding the success of products, fail fast strategy, capacity constraints in Phase III, regulators more risk averse);
- So called “Me-toos” should be valued more than they often are. It is usually not the first product in a class that is the most successful one and different me-toos might offer additional benefits to some patient sub-groups; and
- The expectations with regard to new technology were initially too high.

Reasons identified for the crisis

- The EU is lagging behind the US in terms of development of biologics (approval in Europe is more difficult; lack of venture capital);
- The general business environment was mentioned as an important factor for the choice of location: educated labour force, tax breaks, etc.;
- The cost of innovation has increased (concentration on chronic therapies, more risk averse regulators, ratchet effect regarding the size of trials; requirement to do comparative studies);
- Regarding returns on innovation, parallel imports are seen as a continuing problem for big pharmaceutical companies. The pros and cons of therapeutic reference pricing require careful consideration if it is not to harm innovation further. As there are no major changes in patent regulation, this is not seen as a main driver of changes in innovative activity; and
- M&A may have a short-run detrimental effect on innovation but often leads to long run opportunities to improve research.

Selected Recommendations

- 1) Improvement of the development process could foster innovation (critical path initiative, acceptance of end-point design). This requires better ‘tools’ (European centre for predictive toxicology).

- 2) Greater co-operation and sharing of data could increase the predictability and reduce the cost of developing products that will fail. Although many companies talk about this, there has been relatively little action.
- 3) Better communication is also required between companies and regulators. Europe could learn from the more formal process at the end of phase II undertaken in the US. Generally, it was felt that there is a gap between scientists with the regulators and those with the companies. It was pointed out that smaller companies need “hand holding” by the regulator. There could be performance goals regarding the interaction with industry.
- 4) It was proposed to move from a rules-based approval approach to a more science-based approach. Bringing down the costs of R&D and making costs more predictable was seen as an important feature to improve innovative activity.
- 5) The lack of access to risk capital was seen as an impediment in Europe, in particular for smaller companies. Government intervention can help to alleviate this issue. The G10 idea of a European NIH could be a good idea.
- 6) Although individual pieces of European regulation are working in the right direction, there is a need for European policy to be better joined up.

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