

# The many faces of innovation

A report for the ABPI by the  
Office of Health Economics, March 2012

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## Foreword

The Association of the British Pharmaceutical Industry (ABPI) commissioned the Office of Health Economics to update its 2005 Many Faces of Innovation report (originally commissioned by the European Federation of Pharmaceutical Industries and Associations (EFPIA)). This second edition has the same structure as the first but incorporates much new material. We have updated Chapters 2, 3 and 5 with more recent literature. For Chapter 4 we have provided up-to-date case studies.

## Foreword by Stephen Whitehead, Chief Executive Officer, ABPI

Our modern world owes everything to innovation. Throughout human history it has changed every aspect of our lives, from ancient developments like the printing-press, through to modern day technologies like smartphones. To plot the history of innovation is to plot the history of mankind.

Progress in medicine and healthcare has taken place through countless innovations, from Hippocrates to the present day. The purpose of medical innovation is to fulfil unmet clinical need and recent history has seen rapid advances, with many medicines offering hope to patients with previously untreatable diseases. The pursuit of discovery and improvement in medicine is endless, there are no cure-alls or final answers; just increased understanding. Innovation is the result of continuous study and development and all modern medicines are the product of countless steps forward.

The *Many Faces of Innovation* illustrates examples of where these step-by-step improvements have brought significant benefits to the efficacy and safety of existing treatments, like greater effectiveness in comparison to predecessors; fewer side-effects; easier self-administration, and increased cost-effectiveness.

Incremental developments may also help treat specific patients, as therapeutic alternatives provide healthcare professionals with more choice, enabling them to tailor the patient's medication to their individual needs. This is set to progress further in the future as it will become standard practice to treat an individual rather than a broad disease through the development of new personalised medicines in partnership with effective diagnostics.

The industry invests heavily in R&D in the UK – £12.1 million per day, nearly £4.5 billion per year – to meet unmet medical need. We seek to innovate to resolve human illness and suffering. Our history proves how effective we are as the examples of TB and heart disease will testify. But we need to understand the true nature of innovation in medicine – how it works and how we value it.

Medical understanding is constantly developing and the R&D model – industry, charity and academic – is also always changing. The increased understanding of disease and discovery is generally iterative, but it is punctuated by breakthroughs such as Banting's study of insulin, upon which treatments can be built and tailored. The challenge of recognising and understanding how innovation in medicine works is critical to the future of healthcare.

## Foreword by Richard Bergstrom, Director General, EFPIA

Back in 2005 when EFPIA commissioned the first *Many Faces of Innovation* from OHE Consulting, many countries were implementing a number of cost containment measures for pharmaceuticals. An integral part of these measures relied on some form of assessment of the degree of innovation of new pharmaceuticals. At the time medicines were frequently being characterised as either ‘innovative’ or ‘non-innovative’. EFPIA believed, and still believes, that such a narrow definition of innovation is static and ignores important benefits that medicines can generate. *The Many Faces of Innovation* highlighted all the potential characteristics of innovation for pharmaceuticals. Our objective was to make clear that innovation has many dimensions and is a matter of degree, in an attempt to persuade policy makers internationally to think about innovation more rationally.

*The Many Faces of Innovation* helped move the policy discussion towards considering innovation as a multidimensional phenomenon, rather than just an either/or characteristic. It was translated into a variety of languages by national trade associations and their feedback was that positive discussions with policy makers took place as a result.

But some things never go away. Given the economic situation in 2012, the pressure to constrain public expenditure grows and expenditure on medicines is a favourite target for cost containment by payers. Unfortunately measures are applied across the board with insufficient consideration about the value of medicines to patients and society. There are however, discussions taking place in some countries around linking more, and better, the price of a medicine to its value. A key element is how we define value.

We are particularly grateful to the ABPI for commissioning a second *Many Faces* report. Important discussions are taking place in the UK around its future pricing scheme – the proposed value based pricing system. It is essential that the future system, however it is implemented, recognises the potential attributes of an innovative pharmaceutical industry. This report highlights these attributes, both theoretically and with real life examples. The case studies are impressive, and demonstrate how medicines can be innovative across a wide range of dimensions.

The purpose of this publication is to share that broader perspective of innovation. Progress is often made in incremental steps that may be small but could be vital for an individual person and which accumulate into major progress over time. Everyone involved in the development or evaluation of medicines should appreciate these features of incremental innovation.

## Executive Summary

The objective of this report is to aid understanding of the nature of innovation in the pharmaceutical industry. The following is a fully revised and extended second edition of the 2005 OHE Consulting report for EFPIA, *The Many Faces of Innovation*. We have updated the review of the literature on the economics of innovation. We have taken into account further innovations in classes of pharmaceuticals that were discussed in 2005 and have provided new, more recent, case studies. Finally, we have updated the discussion of dynamic competition in research and development (R&D).

The structure of the report is as follows. We first set the context. The second chapter characterises innovation in general, while the third chapter focuses on the nature of innovation in pharmaceuticals specifically. The fourth chapter provides examples (with detailed references to the published evidence) of several therapy areas to demonstrate pharmaceutical innovation in practice, illustrating the principles described in the preceding chapter. The fifth chapter discusses the possible advantages from dynamic competition between companies even where, and indeed partly because, that leads to having follow-on products in a therapeutic area. Chapter 6 concludes the report.

The context is one of increasing pressure on the pharmaceutical industry to justify itself as innovative, and of growing reluctance on the part of payers in Europe to recognise and reward innovation beyond a very limited definition of the term.

The key characteristics of the R&D process in the biopharmaceutical industry are: there is a high level of uncertainty; the cost of bringing new drugs to the market is high; timelines to develop new products are long; and there are complex interrelationships between organisations involved in pharmaceutical research (private and public sector) that generate positive spillover effects, increasing the yield to R&D efforts.

Innovation is generally characterised in the economic literature as a cumulative process of success. Thus, innovation is a process of evolution, generally proceeding in incremental steps rather than giant leaps. Moreover, innovation is not ‘on or off’, ‘black or white’; rather it is a matter of degree.

Newness alone does not imply innovativeness. It must be combined with consumers’ willingness to pay for it. Thus, under normal market conditions, the consumer is the ultimate arbiter of value, because the consumer is both the end user and the payer.

In the market for prescription medicines, although the consumer/patient may influence the prescribing decision, he or she is not usually the main decision-maker about whether and what medicine to consume – the prescriber takes the major role. Nor is the consumer/patient usually the payer for the medicine consumed, as he or she will only pay a part of the price (via copayments) if at all. The main payer is usually a third party, via tax-funded health services, social insurance or private insurance. This has important implications in terms of how innovation is defined and valued by each of the different agents, as sometimes the different agents will have differing views. For example, a third-party payer concerned primarily about cost may neglect much of the benefit falling beyond the patient and the healthcare system.

There are two key aspects of innovation. First, it is an uncertain activity. Outcomes can only be poorly predicted, if at all. Experience effects are important and successive improvements derive significant economic benefit through experience processes. Hence, second, innovation is a cumulative activity where small steps building on what has gone before are important.

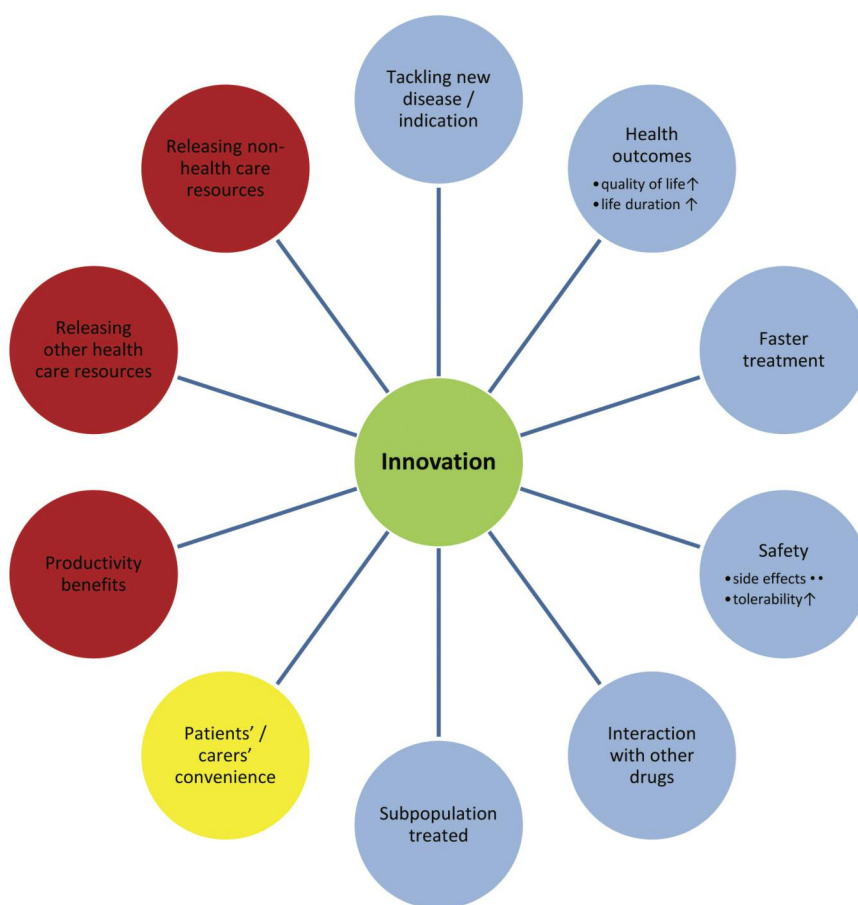
In addition to this, innovation has many dimensions. For these reasons, it is misleading to attempt to categorise the degree of a medicine’s innovativeness as either a ‘breakthrough’ or not. One of the main problems that arise from using a binary classification is the pejorative sense that is then attached to the term ‘incremental’. Innovation in pharmaceuticals should not be classified using this dichotomy,

given its complexity and multi-dimensionality and the importance of cumulative steps to overall innovation. A broad perspective needs to be taken when evaluating innovation in medicines; otherwise, we run the risk of ignoring some, or all, of the advantages of follow-on products.

Figure ES1 summarises the numerous potential attributes of a pharmaceutical innovation that need to be taken into account. The attributes can be grouped under three more general headings:

- Health gains
- Patients' and carers' convenience
- Other societal gains, including cost savings.

**Figure ES1. Potential attributes of an innovative pharmaceutical**



In the report we illustrate with several examples how innovation has been characterised in the pharmaceutical market. These examples, which are evidence-based (key references are cited) and therefore inevitably historical rather than forward-looking, show cases where there were major advances in treatment in areas with no treatment available beforehand, overall benefits of a class, and subsequent benefits achieved by further innovations within the same therapy area as a result of follow-on drugs. The value of any one medicine, or class of medicines, comes from demonstrating the benefit to the patient, carer, payer, prescriber and society as a whole.

There are also advantages from having dynamic competition between companies researching in overlapping areas. These advantages are separate from the characteristics of the individual medicines produced. Dynamic competition advantages have three aspects. First, there is evidence of price competition in different therapeutic areas as a result of having various substitutable treatments available. However, the degree of competition also depends on the incentives for prescribers to take price into account, and on the amount of price freedom – the higher the flexibility, the tougher the competition.



Second, there is competition in pharmaceutical R&D, which implies that pharmaceutical R&D is not a winner-takes-all race: ie the first-in-class medicine may not necessarily be the best in class. This drives efficiency and speed in R&D and means that R&D by different companies is often simultaneous – it is often not possible to distinguish between R&D for first-in-class and follow-on medicines. Given the high risks and uncertainties associated with pharmaceutical R&D, any compound could fall at the next R&D ‘hurdle’. Thus, multiple compounds for any one therapeutic area are needed to ensure that at least one of them is successful.

Third, there are R&D spillovers, which imply that: (1) there is a correlation between a company’s own innovative achievements and the success of rival firms’ efforts; and (2) public medical research and private R&D complement each other.

The scope of this report is limited to providing a clear enunciation of the nature of innovation in medicines. We do not attempt to determine the ‘optimal’ pricing and reimbursement mechanism for medicines. However, we believe that pricing and reimbursement systems need to allow for a broader definition of innovation, either incorporating all of the dimensions outlined or, if not, providing explicit justification for why they are not to be rewarded.

Any policy that does not recognise all aspects of value as well as the costs to the payers, and that has the potential to increase the uncertainty of future earnings if a company fails to launch the first-in-class medicine, might end up discouraging potential worthwhile R&D investment, rather than encouraging it.

# 1. Background and Terms of Reference

Innovation is not, and should not be treated as, a ‘black or white’, ‘there or not’ quality. The marginally more sophisticated approach of trying to categorise new medicines (or any other products) as ‘breakthroughs’, ‘incremental innovations’, or simply as non-innovative, is misleading. New products may be more or less innovative: innovation is a matter of degree, not a quality that is simply present or absent. Innovation should be viewed as a continuum rather than as a discrete on/off quality. Innovation is also multi-dimensional. The greater the improvement on the more dimensions, the greater is the degree of innovation.

The final user is the ultimate arbiter of a product’s value and hence of its degree of innovation compared with pre-existing products. In the pharmaceutical market the final user, the patient, is usually not the payer – there is often a third party payer acting on behalf of the patient. Thus the patient is often unable to give expression to the value he or she places on a medicine, and third-party payers need to take into account patients’ wants and willingness to pay when determining reimbursement of medicines.

There is increasing pressure on the pharmaceutical industry to justify itself as innovative, and growing reluctance on the part of third-party payers in Europe to recognise and reward innovation beyond a very limited definition of the term. Cost-containment policies are being implemented in several pharmaceutical markets based on interpretations of what constitutes ‘innovation’ in medicines. Reimbursement status and/or price depend on the medicine’s deemed degree of ‘innovativeness’. There is a risk that some of these approaches to pricing and reimbursement fail to recognise the value of incremental improvements achieved by new medicines.

An example is the German therapeutic reference pricing system. Medicines considered to be non-innovative, using a limited view of innovation, are included in the reference price system, irrespective of their patent status. Only those patented products judged to demonstrate a significant therapeutic improvement are excluded from this mechanism. The definition of therapeutic improvement being applied by the Gemeinsamer Bundesausschuß is, however, a narrow one.

In Spain, only those products with an ‘exceptional’ innovation level are to be reimbursed with a price premium but it remains unclear how ‘exceptional’ innovation is defined. Italy has introduced an innovation algorithm, where consideration of disease severity, availability of other treatments, and therapeutic effect yields one of three possible therapeutic innovation ratings: important, moderate, or modest.

Under these types of policies, many new medicines with valuable, improved characteristics may be treated as if they are no different from generic copies of existing products. Due to the uncertain and lengthy nature of pharmaceutical R&D, this approach is likely to act as a disincentive not only to incremental improvements on existing products but also to pharmaceutical R&D in general, for reasons that will be explained below.

The UK government has recently proposed that a new ‘value-based’ approach to pricing branded medicines used by the NHS is to be implemented from 1 January 2014. The precise form of this value-based pricing system is yet to be determined, but the Department of Health’s December 2010 consultation document states in its ministerial foreword, and repeats in the body of the document, that the pricing system: ‘aims to recognise and reward innovation, in particular by encouraging a focus towards genuine breakthrough drugs which address areas of significant unmet need’ (DH, 2010). Higher reimbursement prices will be available ‘for medicines that can demonstrate greater therapeutic innovation and improvements compared with other products’ (DH, 2010, paragraph 4.10). But the consultation document belies a way of thinking about innovation that sees it in terms either of breakthroughs or incremental changes. Paragraph 4.25 of the consultation document refers to ‘an appropriately increased incentive to companies to focus their resources on achieving genuine step

changes in clinical performance, rather than seeking just to make incremental changes'. This comment suggests a misunderstanding of the pharmaceutical innovation process, as will be discussed below. Companies and investors do not choose to avoid breakthrough innovations. Rather they can be expected overall to adopt a portfolio approach, seeking a mix of R&D projects with high potential paybacks, even if associated with high risks, along with less risky but probably smaller payback projects (Gordian et al., 2006; Ma and Zimmel, 2002; Pammolli et al., 2011).

Any project can have unexpected outcomes owing to the inherent uncertainty of R&D. Many projects fail to produce marketable medicines, others may look like potential major breakthroughs but end up as valuable but lesser improvements, and yet others may start out looking likely to yield modest improvements but end up as major therapeutic advances. The extent of innovation is unpredictable at the time when resources are committed to R&D.

In many countries an important factor affecting pricing and reimbursement, and hence the signals given to the pharmaceutical industry about whether and where to invest in R&D, is how payers and regulators characterise 'innovation'. There is a risk that an excessively narrow approach to defining innovation could be, or is already being, applied – in particular one which ignores the significant advantages of having more than one product within any one therapeutic area.

A strong motivation of this paper is to aid understanding of the process of innovation in the pharmaceutical industry. This understanding is needed in order to provide the right economic incentives to generate socially-valuable R&D. We need to avoid those regulations and hurdles that kill projects with the potential of becoming socially-valuable innovations in the future. Policies that aim to restrict the number of medicines available in any one therapeutic area can reduce incentives for investment in innovation, given the uncertainty of the R&D process – the characteristics of a new medicine take time to become fully understood and may even not become fully known until after it has been marketed. Further, having a choice of medicines within any one therapeutic class is also important because if one medicine does not show efficacy or safety in a particular patient then another medicine in the same class often will.

For this reason, it is important to highlight here four key characteristics of the R&D process in the biopharmaceutical industry. First, there is a high level of uncertainty due to a significant scientific challenge at early stage (basic research and pre-clinical) and recurrent risk of failure at clinical phases.

Second, timelines to develop new products are long – on average it can take between six and seven years for the clinical testing (so-called Phases I, II and III) plus two more years for the regulatory approval process (Scherer, 2010). Partly as a result of these first characteristics, the pharmaceutical sector is R&D-intensive – indeed the highest R&D intensive sector, as shown by the EU Commission latest research scoreboard (EU Commission, 2009).

Third, the cost of bringing new drugs to the market is significantly higher compared to other sectors. Recent estimates place the out-of-pocket costs of developing a new product at between \$150m and \$200m, in 2009 prices (DiMasi et al., 2003; Paul et al., 2010), whilst in other highly innovative sectors, such as IT and communications technologies, the cost of bringing new products to the market is around £4 million (Cooksey, 2006). Note that the \$150-\$200m estimate for new drugs does not include either the cost of failures (the resources spent on ultimately unsuccessful R&D projects) or the cost of capital, which is large given the length of time required to get through the entire R&D process. Taking these two factors into account raises the total cost of developing one successful compound to the region of between \$800m (DiMasi et al., 2003) and \$1.7bn (Paul et al., 2010), in 2009 prices.

Fourth, there are increasingly rich linkages between the private sector, on one hand, and academic science carried out in universities and governmentally-supported research institutions on the other, both in countries where companies operate and across national boundaries (Scherer, 2010). For example, Marston (2011) shows that biomedical papers that are co-published with industry have greater citation impact than purely academic papers.

The 'linear model' of innovation was originally conceived as industrial innovation proceeding from basic research to applied research and then to development and commercialisation. Under this traditional model, public (and charitable) research would take place upstream of private R&D. However, during the past two decades, a richer characterisation of the innovation process has been developed, as a more interactive relationship between the public (and charitable) and private elements of research (Cohen et al., 2002). Martin (2010) argues that the move from the linear model to an interactive 'chain-link' model of innovation, as originally conceived by Kline and Rosenberg (1986), is one of the 20 most important advances in science policy.

The relationship between reimbursement mechanisms and rewards for innovation was discussed in the WHO Priority Medicines Report (WHO, 2004). This report argues, among other things, that pharmaceutical cost containment in Europe is achieved by setting prices at levels that do not fully reward innovation and by delaying decisions about reimbursement. These problems lead to uncertainty among stakeholders and encourage companies to launch their products first in non-European markets.

The purpose of the remainder of this paper is to set out all of the potentially valuable aspects of innovation in medicines, including incremental innovation and added therapeutic value, and to provide examples of products that illustrate the different kinds of innovation and added value.

The structure of the paper is as follows. Chapter 2 describes how innovation in general is characterised in the literature. Chapter 3 characterises innovation in pharmaceuticals, while Chapter 4 illustrates with examples how our characterisation of innovation works in practice. Chapter 5 discusses the potential (economic and social) value of having additional follow-on products, and the final chapter concludes the document.

## 2. Defining and Characterising Innovation in General

Innovation is generally defined as a process concerning ‘the search for, and the discovery, experimentation, development, imitation, and adoption of new products, new process and new organisational set-ups’ (Dosi, 1988). It covers a variety of disciplines, including science, economics, corporate management and marketing, as it proceeds through ‘the exploration and exploitation of opportunities for a new or improved product, services or processes’ (Pavitt, 2003). Thus a discovery or invention drawing from basic and applied research becomes an innovation if it is implemented in the market or used within the production process, and is adopted by other parties beyond the discoverers. Innovation implies an advance that is not merely technological but which also brings social and economic consequences. Further, the concept of diffusion of innovation relates to the efforts of buyers and competitors to introduce the new products, processes or services; and diffusion generally leads to further innovation on the part of developers and users (Dosi and Nelson, 2010).

In sum, invention relates to unexploited potential for technological progress, while innovation and diffusion relate to economically-motivated efforts aimed at incorporating technological advances into economically-exploitable products, services or processes (Dosi and Nelson, 2010).

Innovation is generally characterised in the literature as a cumulative process of success. As expressed by Dosi and Nelson (2010): ‘Innovative advances are made by dwarfs standing on the shoulders of past giants’. Thus, innovation is a process of evolution, generally in incremental steps rather than giant leaps. Moreover, innovation is not ‘on or off’, ‘black or white’; rather it is a matter of degree. The view that innovation is a multidimensional process is also suggested by Whyte (2011), who argues that innovation is ‘as much about finding new ways of using or delivering existing goods and services as about producing new ones’.

Innovation happens in all areas of economic activity. However, firms have been the economic entities that employ most new technologies, produce and market new products and services, and operate new production processes. Firms’ organisational knowledge links the ‘social pool’ of knowledge, skills, and opportunities of discovery, with the efforts aimed at their actual exploration (Dosi and Nelson, 2010). Where firms operate in effective consumer markets, it is the ultimate consumers of goods and services who determine whether a new product is innovative or not. Newness alone does not imply innovativeness; it must be combined with consumers’ willingness to pay for it. Thus, under normal market conditions, the consumer is the ultimate arbiter of value, because the consumer is both the end user and the payer. Kay (2011) also argues that innovation should not be confused with novelty – innovation is about finding new ways of meeting and creating consumer needs. Indeed, Kay argues that understanding the needs of customers is what distinguishes innovation from novelty. Furthermore, innovation, he argues, should not be conflated with R&D. In practice, the value of an innovation is commonly not fully recognised when the invention is made or introduced. It can take time before potential consumers in a particular market appreciate the whole value of an innovation.

In the market for prescription medicines, although the consumer/patient may influence the prescribing decision, he or she is not usually the main decision-maker about whether and what medicine to consume – the prescriber takes the major role. Nor is the consumer/patient the payer for the medicine consumed, as he or she will only pay a part of the price if at all (via copayments). The main payer is usually a third party, via tax-funded health services or social insurance or private insurance. As a result, consumers/patients and prescribers are often relatively unconcerned about costs. Asymmetric information problems make it difficult for clinicians and patients to assess the cost-benefit ratio of pharmaceutical innovations. Therefore, it is rather difficult to use market forces to determine the innovativeness of new medicines.

It is also important to distinguish between costs that are borne and benefits that are appropriated from pharmaceutical innovation. Benefits are appropriated by the patient and the innovator, while there are costs and benefits that accrue to the rest of society, via externalities and spillovers. A third-

party payer concerned primarily about cost may neglect to take into account much of the benefit falling beyond the patient and the healthcare system, for example cost savings to patients' carers or the economy generally.

Moreover, the third-party payer generally has a fixed budget. This implies that in addition to the willingness to pay of consumers/patients for new medicines, the third-party payer needs to consider the forgone benefits to other consumers/patients whose care they must fund from a limited budget (ie the opportunity cost). For example, in England and Wales, the statutory duty of the National Institute for Health and Clinical Excellence (NICE) is to preserve the interests of all patients, based on the principle of collective needs, in the context of a fixed amount of money (Kennedy, 2009).

## **2.1 Drivers of Innovation**

Any firm considering a potential investment decision with the ultimate objective of launching a new innovative product needs a positive expected net present value for this product – ie its (discounted) expected net future earnings needs to outweigh its (discounted) R&D and other costs. The drivers of innovation presented in this section all have the potential to affect these financial conditions for innovation.

Innovation involves a continual matching process between technological and organisational practices of the innovator, and is driven by a combination of the following:

- Market forces and demand
- Institutional incentives and hurdles
- Scientific knowledge and technological opportunities.

We review these in turn.

### **2.1.1 Market Forces and Demand**

Commercial innovation is substantially driven by demand-side factors: what consumers may be willing to pay, or pay more, for. Certainly, the innovation process undertaken by profit-motivated agents involves perception of an unexploited economic opportunity and an expectation that there exists a market to justify the R&D outlays.

Some authors emphasise the role of 'demand-pull' factors (see Schmookler, 1966) and have provided empirical evidence on the primacy of market demand forces within the innovation process. However, the appeal to demand-pull arguments does not always provide a useful insight into the complexity of the innovation process, which not only might respond to existing patterns of demand but can also create new demands previously unrecognised by the consumer. For example, in the late 1970s, households did not perceive the home computer as a useful item and could not remotely anticipate how many applications it could have. Garcia and Calantone (2002) highlight that new technology 'acts as the catalyst for the emergence of new markets and/or new industries'.

Firms innovate in order to obtain profits. Introducing an innovation allows a firm to gain a temporary competitive advantage, which can originate from a patent or the length of the imitation process by competitors. Schumpeter's famous analysis of technical change sees the innovation process as the modus operandi of the market: firms compete through innovation as well as on price (Schumpeter, 1942). However, Schumpeter's model excludes the role of uncertainty associated with new technologies, by assuming that an innovator firm has only to introduce a new technology into the market in order to profit. Rosenberg (2001) goes beyond this simplified model of innovation. His model acknowledges that the innovation process involves a fundamental element of uncertainty, especially with respect to the ultimate characteristics and hence the market value of any products that come out of it.

### **2.1.2 Institutional Incentives and Hurdles**

National institutions and structural conditions determine the broad parameters within which innovative activities are carried out. This general institutional environment, which comprises

legislative settings, financial institutions, educational systems and the functioning of labour markets, affects the innovation process by setting the rules and range of opportunities for innovation (OECD/Eurostat, 1997):

- Innovation generally requires a wide array of public and private investments. Government direct and indirect support to the private sector's R&D is important because returns are uncertain and/or because the private innovator may not be able to appropriate (ie be paid for) all of the benefits. This is particularly important in the life sciences sector.
- Legislative settings can result in barriers to entrepreneurship. A number of common barriers to entrepreneurship activity in OECD countries include regulatory and administrative opacity, administrative start-ups and barriers to competition (OECD, 2010).
- The educational system is important because it provides (or not, as the case may be) appropriately skilled labour, such as doctoral graduates in key areas of science.

Edquist and Johnson (1997) observe that the institutional set-up shapes innovative activities by:

- Reducing uncertainty, as it can provide information and increase the degree of economic appropriability of innovation
- Managing conflicts and aiding cooperation, as it can ensure stability and respect of societies' rules, and support the economic restructuring necessitated by high rates of innovation
- Providing incentives, both pecuniary (eg wage schemes, tax allowances, intellectual property rights, government subsidies for R&D) and non-pecuniary (eg prestige, status)
- Introducing obstacles, such as rigid rules that have to be complied with.

In addition, institutions may help to channel resources to specific areas, in particular through collaborative sponsored programmes for R&D (Pavitt, 2003).

### **2.1.3 Scientific Knowledge**

Technological innovation exploits scientific knowledge, which can provide an essential understanding and theoretical base for business innovation. On the one hand, the body of knowledge determines the opportunities for technological progress and suggests possibilities for designing new products or improving the performance of existing ones, or for producing those products at lower costs. On the other hand, historical examples have shown that, in turn, technical needs have influenced and stimulated scientific activity in numerous and pervasive ways. A famous example is Louis Pasteur's development of the science of bacteriology, which 'emerged from his attempt to deal with problems of fermentation and putrefaction in the French wine industry' (Rosenberg, 1982).

The creativity and intuition of researchers can also be an important scientific driver of innovation. Furthermore, serendipity, defined as the act of finding answers to questions not yet posed (Stephan, 2010), plays a major role in the process of scientific knowledge production and innovation. There are numerous examples cited by Stephan (2010): for instance, a scientist studying marine snails found a powerful new drug for chronic pain; and the discovery of AGM-1470 – a drug being tested for an entirely different approach to the treatment of cancer – was described as the result of a 'laboratory accident'.

### **2.2 Innovation is an Uncertain Activity**

The innovative process, involving the activities of search and experimentation, entails major uncertainty, so that its outcome can barely be anticipated ex ante. Innovators aim to develop and exploit technical and economic opportunities, the performance and cost of which cannot be accurately predicted in the early stages of the innovative process. Even after a new technology has proven to be workable and has been brought onto the market, it is difficult to forecast:

- Its eventual social and economic impact (in particular, its valuation by users and consumers, and its positive and negative externalities that affect society)
- The possible directions of the technology changes (technical improvements, cost reductions, competition with old and new technologies).

Connected to the uncertain impact of innovation is ‘the inability to predict the rate at which performance improvements and cost reduction can take place, as well as the speed with which new uses are discovered for new capabilities’ (Rosenberg, 2001). Pavitt (1987) notes that: ‘theory is rarely sufficiently robust to predict performance of a technological artefact under operating conditions and with a high enough degree of certainty, to eliminate costly and time-consuming construction and testing of prototype and pilot plant’. Technological improvements and cost reductions may result in price declines and technology diffusion but they may also encourage improvements of old technologies and introduction of yet newer ones.

Uncertainty plays an important role in the way that R&D is conducted in the pharmaceutical industry, and more generally in other R&D-intensive industries. For example, when safe and efficacious molecules cannot be identified in advance, it is often desirable to pursue a parallel path strategy, ie synthesising and testing alternative molecules at the same time. The lower is the probability of success for any single R&D path, the larger are the benefits of having multiple R&D research paths. Moreover, parallelism in this industry can occur across competing firms (Scherer, 2010), which Cockburn and Henderson (1994) call competition ‘racing’.

Furthermore, when managing a group of research projects, the skewedness of the distribution of rewards from innovation – a few projects yield very large rewards, many products yield only small or no rewards – makes it difficult for a firm to hedge against risk. This is a standard feature of high - technology investment strategies (Scherer, 2010).

### **2.3 Innovation is a Cumulative Activity: Small Steps are Important Too**

The fact that new technologies come into the market in a primitive form which can be improved and widely adopted only after its first introduction highlights another important aspect of innovation: successive improvements. As Lipsey and Carlow (1998) argue, ‘major radical innovations never bring new technologies into the world in a fully developed form. Instead, these technologies first appear in a crude and embryonic state with only a few specific uses.’ Successive improvements accumulate through experience in production, and derive a significant economic impact through the processes of ‘learning by doing’ and ‘learning by using’:

- ‘Learning by doing’ occurs at the manufacturing process level as workers improve their skills in making the product (Arrow, 1962).
- ‘Learning by using’ improvements originate from the utilisation of the new technology by the final user. The importance of this aspect of learning is particularly important when the scientific knowledge or techniques cannot predict accurately some performance characteristics (Rosenberg, 1982). For example, much of the essential knowledge in aircraft design and construction derive from in-flight learning. Indeed the ‘extensive use of an aircraft may eventually lead to the discovery of faults in components or design, as in the discovery of metal fatigue that led to considerable loss of life in the Comet, or the unusual resonance that eventually weakened the engine mounts of the Electra and also led to fatal crashes’ (Rosenberg, 1982).

Complementary to the learning aspects is the cumulative and iterative nature of innovation. Rosenberg (1982) highlights that ‘the total growth in productivity takes the form of a slow and often invisible accretion of individually small improvements in innovation’.

There is a tendency to associate major innovations with an individual inventor at a precise date. But that is misleading. It is important to understand the cumulative impact of the many small improvements that



occur over time which help to meet the needs of users better than the early versions of a product. Kline and Rosenberg (1986) provide the example of electric power generation, which has one of the highest rates of growth of total productivity in the twentieth century although no single major innovation occurred. These authors argue that 'slow cumulative improvements in the efficiency of centralised thermal power plants have generated enormous long-term increases in fuel economy'.

All these characteristics of innovation are well summarised by Kline and Rosenberg (1986), who point out that 'it is a serious mistake to treat innovation as if it were a well defined, homogenous thing...the subsequent improvements in an invention after its first introduction may be vastly more important, economically, than the initial availability of the invention in its original form' (pp. 283).

### 3. Characterising Innovation in Pharmaceuticals

Innovation in the pharmaceutical industry is a complex phenomenon that significantly contributes to society's wellbeing and health. It involves different stakeholders (industry, patients and their carers, physicians, academics, governments, international organisations) and its influence is not restricted to the pharmaceutical sector but is crucial for the entire economy. Innovation in the pharmaceutical industry brings benefits to the economy and society and not just to the patients receiving the medication, as argued below. In addition, resources used by the industry to develop new drugs bring value to the country where the industry is located.

Innovation has many dimensions, all of which need to be considered by third-party payers designing pricing and reimbursement policies for medicines. An aspect of value that is insufficiently rewarded will in future, other than by off-chance, be insufficiently produced. If pricing and reimbursement policymakers determine not to reward an aspect of value, they should be open about their reasons for not doing so.

New medicines are commonly referred to as being either a 'breakthrough' or a 'me-too'. Under this simplistic classification, a breakthrough or major innovation is defined as a first agent with a particular clinical action or pharmacological action, or the first with the same clinical effect as existing agents but a different mechanism of pharmacological action. 'Me-too' or incremental innovation is then defined as a follow-on modification in molecular structure or dosage formulation having similar, but not identical, pharmacological action or a different absorption, metabolism or excretion profile.

One of the main problems that arise from using this binary classification is the pejorative sense attached to the term 'incremental'. Innovation in pharmaceuticals should not be classified using this dichotomy, given its complexity and multi-dimensionality and the importance of cumulative steps to overall innovation, as discussed in Chapter 2 of this paper. A broad perspective needs to be taken when evaluating innovation in medicines; otherwise, we run the risk of ignoring some, or all, of the advantages of follow-on products.

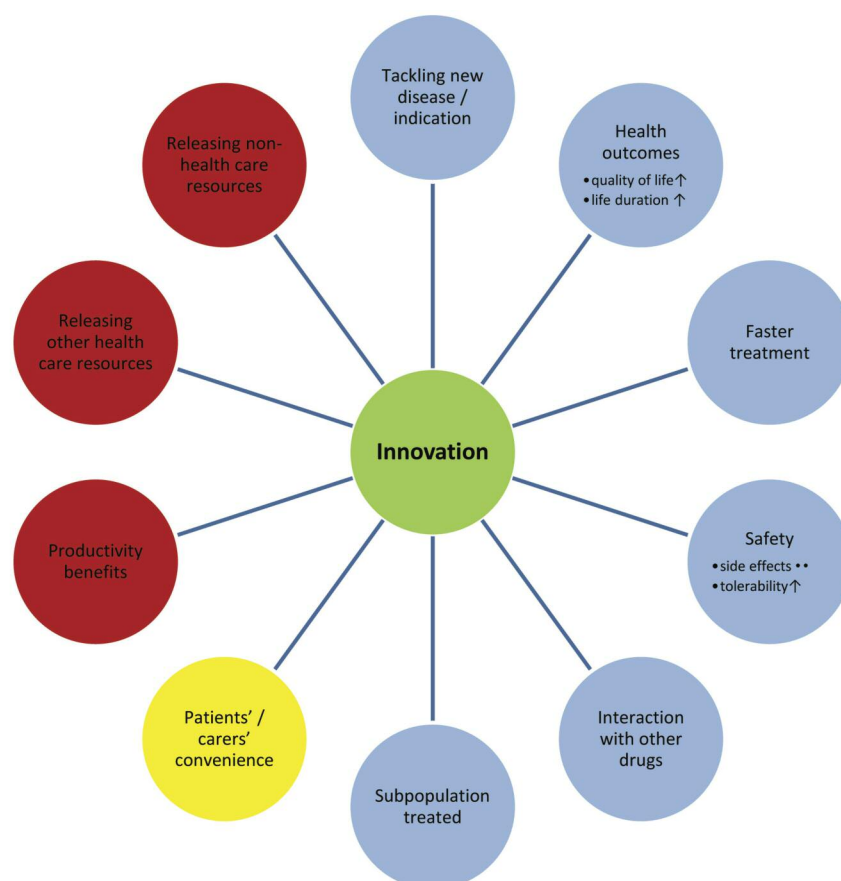
We have already explained that an invention becomes an innovation when it is successfully implemented and adapted in the market place. This implies that consumers, as final users and payers, have both to value an innovation and be willing to pay for it. For pharmaceuticals, however, there is a need to make a distinction between the final consumer (ie the patient) and the payer, as these often do not coincide. Thus, any innovation in the pharmaceutical industry can either derive an improved benefit-cost ratio for the patient, or have a positive effect for the payer by reducing costs, or both. As stated in the Kennedy Report to NICE, innovation is referred to as connoting 'different ways of doing things which bring improved outcomes' (Kennedy, 2009).

Figure 3.1 summarises the numerous potential attributes of a pharmaceutical innovation that need to be taken into account. The attributes can be grouped under three more general headings:

- Health gains
- Patients' and carers' convenience
- Other societal gains, including cost savings.

Examples in practice of all the possible elements of innovation shown in Figure 3.1 are presented and discussed in Chapter 4.

**Figure 3.1. Potential attributes of an innovative pharmaceutical**



Under the heading 'health gains' (shaded blue in Figure 3.1), improvements in any of the following dimensions as a result of introducing a new medicine can imply an innovation:

1. Tackling any new disease and/or indication
2. Health outcomes (gains) as compared to existing treatments, which may comprise one or both of quality of life and quantity of life, both for patients and carers
3. Faster health improvement, eg reductions in recovery time from weeks to days may be valuable to patients even if too small to be detected by traditional measures of outcome – quality-adjusted life years (QALYs)
4. Reduced side-effects and/or improved tolerability (which leads to better health gains for patients both directly and through better adherence)
5. Reduced negative interactions with other medicines
6. Possibility of better treating one or more different patient subpopulations, with the advantage that patients are less exposed to one-size-fits-all medicines.

Health gains can arise either when a new medicine starts treating a new condition not hitherto prevented or treated effectively (ie first-in-class) or by offering some form of health gain versus existing treatments. Not all medicines are life-saving, but some offer relief and/or improvements in quality of life.

'Patients' / carers' convenience' (shaded yellow in Figure 3.1) includes any attributes which improve patients' and carers' experience of the process of healthcare and hence their satisfaction, independent

of the final health outcomes. Examples of such attributes can include new presentations or delivery methods of existing molecules, such as patches, or oral treatments replacing intravenous; the opportunity for patients to treat themselves at home instead of having to go to the hospital and/or physician; and special pharmaceutical presentations for children, the disadvantaged and those affected by inequalities in health and health care. As a result of improved convenience, patients may also enjoy greater independence and greater dignity.

Patients' convenience is an aspect of innovation because it is something the end user would be willing to pay for, given the chance. Greater convenience is a desirable end in itself from the patient's perspective, and as a result it should also lead to better compliance and hence to further health gains. Better adherence can also lead to cost reductions by avoiding the waste that arises when patients do not comply with their treatments.

'Releasing other healthcare resources', 'releasing other non-healthcare resources', and 'productivity benefits' (shaded red in Figure 3.1) are benefits that accrue to the payers for healthcare services (whether third-party payers or patients and carers paying out of their own pockets), or to the economy as a whole. Other resources can be freed as a result of the introduction of new medicines, now or in the future through disease prevention and/or slower progression of the condition. If new medicines enable a change in the way that healthcare is provided to a group of patients then other resources (including non-healthcare resources, such as social care) may be released. An example is when medicines reduce hospitalisation costs by reducing lengths of inpatient stays or by eliminating the need for hospitalisation altogether. It can also be the case that medicines will improve the cost/benefit ratio relative to existing treatments. Other non-healthcare resources could include reduced patient/carer out-of-pocket costs and costs falling on other jurisdictions, such as formal social care and the criminal justice system. New medicines can also lead to productivity gains as a result of patients or carers returning more rapidly to work or not missing work at all, or to them being more productive when they are at work, or to carers being able to lead a more independent life.

Chapter 4 of this paper (below) illustrates with examples how individual medicines or classes of medicines bring about improvements in the dimensions shown in Figure 3.1. Not all of the medicines discussed bring improvements in all dimensions, but improvements in any of the dimensions can be socially valuable, which is a point that needs emphasising.

Figure 3.1 characterises innovation as a multi-dimensional phenomenon at any one point in time, ie it represents a snapshot in time. But we need, as discussed in the previous section, to take a dynamic view when we consider the benefits that might arise as a result of new medicines coming into the market. Regarding the experience effects previously described (learning by doing and learning by using), it is the process of 'learning by using' that is of particular importance in the pharmaceutical market. After a medicine is launched and used in real-life settings, two types of improvement can result:

- Better use for the original indication
- Additional indications.

Kettler (1998) shows how experience gained after market approval can lead to new or better uses of the same products. There are three main routes:

1. New formulations, new dosage forms or new forms of administration can provide improved safety and efficacy or extend the range of indications in the original therapeutic area
2. There can be an extension of therapeutic areas of use by application of known pharmacological actions
3. There can be unexpected new therapeutic uses discovered mainly by chance.

Gelijns and Moskowitz (2000) reinforce the last point by arguing that innovation in general, and in medicines in particular, involves serendipity in addition to a great deal of experimentation and creativity. Thus there is an element of uncertainty not only at the R&D stages but also long after new products are introduced into practice. They argue that many new indications have been discovered only after drugs and devices have been introduced into clinical practice. Gelijns and Moskowitz show that for the top 20 best-selling drugs in the US in 1993, by 1995 40 per cent of their revenues were coming from secondary indications. Pritchard et al. (2000) undertook a similar analysis for the top 50 UK products and found that secondary indications accounted for a smaller but still significant 25 per cent of sales. However, Pritchard et al. (2000) find a skewed distribution, with a significant number of products having no subsequent indications but a few others having very substantial use.

Rosen and Beerman (1999) classify the degree of innovation for the new molecular entities introduced in Sweden in the period 1987-1997. One of their main conclusions was that there were important differences observed between therapeutic designations made pre- and post-marketing. They argue that any exercise with the aim of rating innovation in medicines should recognise the realities of post-marketing experience.

For any particular medicine or family of medicines the relevant attributes can change over time, both positively and negatively. The importance of 'learning by using' in the pharmaceutical market implies the need for an element of flexibility in any definition of innovation in order to capture the (un)expected medical benefits revealed through market use.

## 4. Innovation in Pharmaceuticals: Examples

This chapter illustrates with examples how innovation can be characterised in the pharmaceutical market. The first part of the chapter discusses older examples, while the second part focuses on more recent introductions.

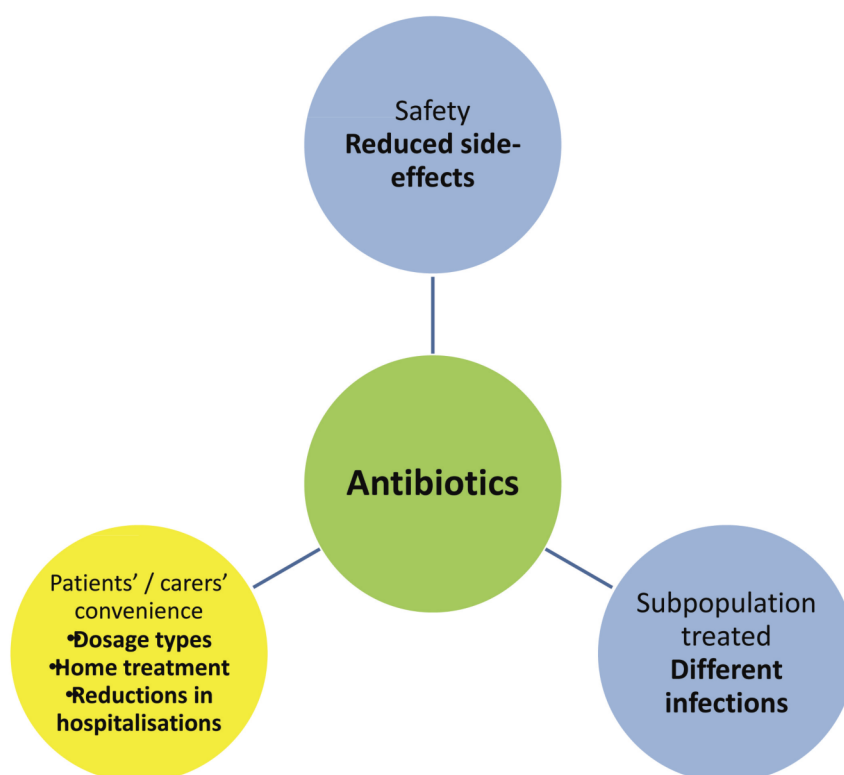
### 4.1 Examples of Innovation in Older Medicines

#### *Antibiotics*

The antibiotic penicillin G was first obtained in 1940. It had several limitations in its use, and as a result several modifications of antibiotics were developed, enabling them to be used in a wider context.

In addition, new antibiotics, including cephalosporins, were developed to respond to the emergence of antibiotic-resistant bacterial strains. The first cephalosporin, introduced in the 1960s, had a broader spectrum of antibacterial activity than penicillin G but was poorly absorbed orally and caused pain by intramuscular injection (Landau et al., 1999). There are now four generations of agents in this family of antibiotics, all representing chemical modifications of the basic cephalosporin structure. Each generation has been able to provide therapy for different types of infection, different infection sites, and different subpopulations of patients. In addition, they are available in different dosage types and in injectable, topical and oral forms, which can improve patients' convenience. Innovations in antibiotics have allowed administration once every day, giving patients the possibility of being treated at home, or at least reducing their hospitalisation time. These improvements obviously have the potential to increase patients' quality of life and save healthcare costs. Figure 4.1 shows the innovations schematically, highlighting the elements of Figure 3.1 that are most relevant to the progressive improvement of antibiotics.

Figure 4.1. Evolution of antibiotics



Source: Adapted from Wertheimer et al. (2001)

### ***Antihistamines***

Second-generation antihistamines have several improvements over first generation antihistamines: less frequent dosing, no anticholinergic side-effects, and limited sedation. Less frequent dosing implies an improvement for the dimension 'Patients' convenience' (cf Figure 1) while the other two advances represent an improvement for the dimension under the heading 'Safety'. Third-generation antihistamines are being developed, based on the second-generation agents. The new generation can bring about improved tolerability, improved pharmacokinetics, fewer side-effects and greater safety (Wertheimer et al., 2001). The reduction in sedation effects has reduced work-related accidents and lost productivity.

### ***Anti-tumour anthracyclines***

Anti-tumour anthracyclines have been used now for several years for the treatment of solid tumours. The second in class substance of this family can deliver lower side-effects relative to the prototype of the class, which improves the safety profile.

### ***Corticosteroids***

The first synthesised corticosteroid was developed in 1949 and used for rheumatoid arthritis. Since then, there have been several modifications that have led to compounds having different potency levels and different durations of action. This demonstrates that the use of such medicines can lead to more tailored and personalised treatments based on the disease being treated and the needs of the individual. In addition, the possibility of delivering corticosteroids by inhalation has the potential to improve safety, tolerability and patients' convenience.

## **4.2 More recent examples**

The case studies that follow are in alphabetical order.

### ***Anti-acids: from H2-receptor antagonists to proton-pump inhibitors (PPIs)***

Inappropriate levels of gastric acid underlie several widespread pathological conditions, including gastroesophageal reflux disease, for which heartburn is the most common symptom, and peptic ulcers. Until the late 1970s, the treatment options for these conditions were very limited – either they only offered temporary relief or patients needed an operation, with serious side-effects.

In the late 1970s, the first antagonist of the H2-receptor, which plays a key role in one of the pathways leading to gastric acid secretions, was made available: cimetidine. Cimetidine was approved in the UK in 1976 and in the US in 1979. It was followed by the introduction of ranitidine, which had a far-improved tolerability profile (ie fewer adverse drug reactions), a longer-lasting action, and caused fewer side-effects than cimetidine (Ranitidine, 2011). The introduction of these drugs considerably improved the lives of millions of people and reduced the need for surgery. But H2-receptor antagonists have limited efficacy: there was high inter-individual variability in response to therapy with them, there was acid rebound, tolerance developed, they had a relatively short duration of action, and they were relatively ineffective in the treatment of reflux oesophagitis (Lindberg et al., 2003; Lindberg and Carlsson, 2006). These are major drawbacks.

The development of omeprazole, the first proton pump inhibitor (PPI), marked a major step forward in the management of acid-related diseases (Carlsson et al, 2002). It was in 1988 that omeprazole was registered in Europe for treating duodenal ulcer and reflux oesophagitis and 1990 in the US. Omeprazole's development was the result, among other things, of an earlier PPI, timoprazole, which had to be discontinued because of toxicity problems (Lindberg and Carlsson, 2006). But, as argued by Carlsson et al. (2002), the unique mechanism of action of timoprazole encouraged pursuit of related compounds. Moreover, elucidating the mechanism of action of omeprazole was spurred on by competition among a number of pharmaceutical companies (Lindberg, 2007).

The inhibition of gastric acid was considerably greater with omeprazole than with the H2-receptor blockers. Moreover, patients with Zollinger-Ellison's syndrome (gastrin producing tumour) could be treated medically without total gastrectomy and gastric surgery with Billroth I and II operations, and surgical procedures for gastric vagotomy were also no longer needed.

The range of related indications approved for omeprazole increased over time – especially in the 1990s, when the full therapeutic potential of omeprazole became apparent. Acid is currently understood to have a central role in a much broader range of gastro-intestinal diseases. Omeprazole has to date been recommended by the EMA for the following indications (EMA, 2010):

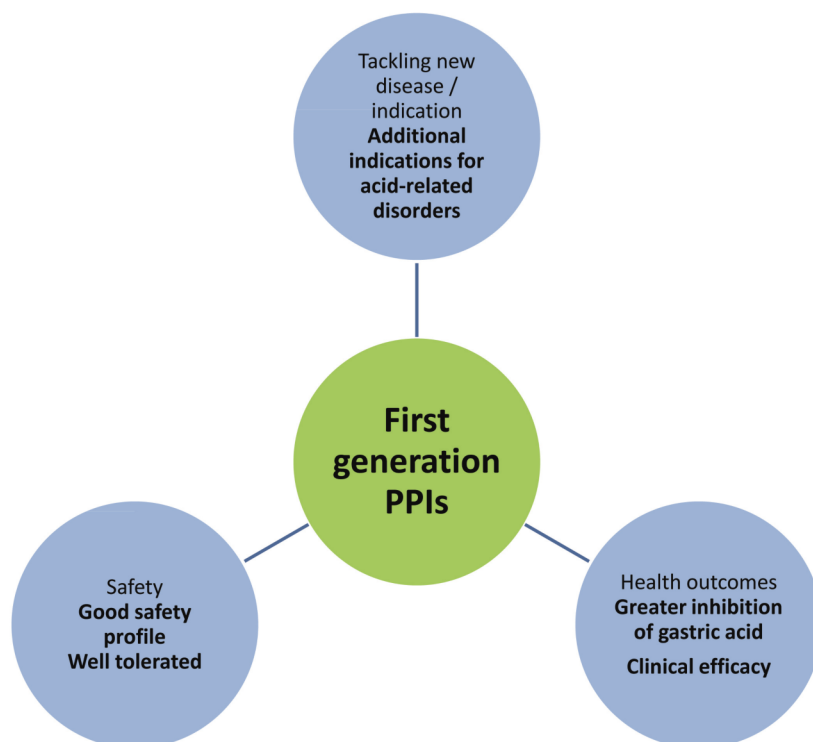
- In adults: duodenal ulcers (treatment and prevention of relapse); stomach ulcers (treatment and prevention of relapse); *Helicobacter (H.) pylori* eradication in stomach and duodenum ulcer disease in combination with antibiotics; non-steroidal anti-inflammatory drugs (NSAID) associated ulcers (treatment and prevention); reflux oesophagitis (treatment, including long-term management after healing); symptomatic gastro-oesophageal reflux disease; and Zollinger-Ellison syndrome.
- In children: reflux oesophagitis; heartburn and acid regurgitation in gastro-oesophageal reflux disease; and in combination with antibiotics in the treatment of duodenal ulcer caused by *H. pylori*.

During the 1980s, about 40 pharmaceutical companies were investigating the development of PPIs, but only a few were successful. Omeprazole was followed by other PPIs, including lansoprazole, pantoprazole and rabeprazole, all built on the same basic structure.

Extensive clinical experience has shown omeprazole to have a good safety profile and to be well tolerated (Creutzfeldt, 1994; Joelson et al., 1992; Solvell, 1990). A comparison of the common adverse events reported during treatment with PPIs in general practice in England showed that they were infrequent and that there were only small absolute differences in event rates between omeprazole, lansoprazole and pantoprazole (Martin et al., 2000).

Figure 4.2a shows the additional benefits over H<sub>2</sub>-receptor blockers of the PPIs – including omeprazole, lansoprazole, pantoprazole and rabeprazole but excluding esomeprazole (which is discussed below).

**Figure 4.2a. Additional benefits of the first generation of PPIs (including omeprazole, lansoprazole, pantoprazole and rabeprazole) over the H<sub>2</sub>-receptor blockers**



*Sources: Adapted from Solvell (1990); Joelson (1992); Creutzfeldt (1994); Martin et al. (2000); Carlsson et al. (2002)*



Although omeprazole provided more effective control of acid secretion than previous therapies, it was not equally effective in all patients. A significant number of patients with acid-related disorders required higher or multiple doses to achieve symptom relief and healing of oesophagitis (Lindberg and Carlsson, 2006). For this reason there was a need to have an even more effective control of acid secretion. The developer of omeprazole screened several hundred compounds with this purpose. The result was esomeprazole, the S-isomer of omeprazole, which is the first PPI available for clinical use as a single isomer. Esomeprazole was the only successful compound of four that were progressed beyond clinical pharmacological studies and tested in patients by this company (Lindberg et al., 2003). Esomeprazole was launched in Sweden in August 2000 and in the rest of Europe during the autumn that year. It was approved and launched in 2001 in the US. Currently esomeprazole has a number of approved indications (eMC, 2011) and has achieved greater inhibition of gastric acid than omeprazole (Carlsson et al, 2002).

Esomeprazole has demonstrated pharmacological and clinical benefits beyond those seen with the racemic omeprazole, resulting in a greater 'area under the plasma concentration-time curve (AUC)' (Andersson et al., 2000; Andersson et al., 2001; Lind et al., 2000). It is the AUC value of each PPI that determines how much of the drug reaches the parietal cell, and is therefore a major factor in determining the control of gastric acid secretion achieved. Esomeprazole has higher and more consistent bioavailability than omeprazole. Esomeprazole provides more effective control of gastric acid secretion than omeprazole and all other PPIs. This translates into greater clinical effect compared with other PPIs in the management of reflux disease. There is also reduced inter-patient variability with esomeprazole relative to omeprazole.

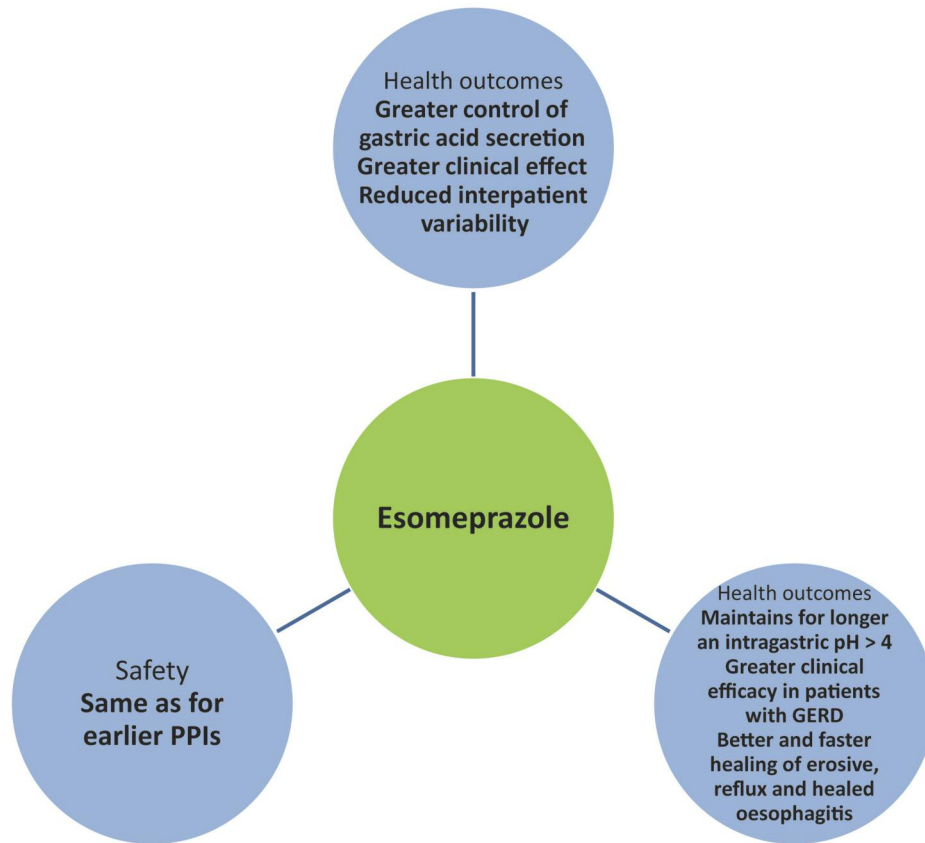
Esomeprazole therapy is well tolerated, with a low adverse-events profile, similar to that seen with omeprazole (Lindberg et al., 2003).

Esomeprazole also maintains an intragastric pH > 4 (this value being chosen because it is the critical threshold of acid control for the effective management of gastro-oesophageal reflux disease) for significantly longer during the subsequent 24-hour period than did standard doses of lansoprazole, pantoprazole and rabeprazole, and these differences became apparent from the first day of dosing (Lindberg et al., 2003). The superior acid control achieved with esomeprazole has been shown to translate into greater clinical efficacy in patients with gastro-oesophageal reflux disease relative to omeprazole and lansoprazole. With esomeprazole, erosive oesophagitis was healed at week 8 in significantly more patients and provided the sustained resolution of heartburn more rapidly and in significantly more patients compared with patients treated with omeprazole (Kahrilas et al., 2000; Richter et al., 2001b).

Similarly, esomeprazole was significantly more effective than lansoprazole in the healing of reflux oesophagitis at 4 and 8 weeks, and sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole. Esomeprazole has also been shown to be highly effective when given as maintenance therapy for healed oesophagitis, and is significantly superior to lansoprazole in maintaining remission across all pre-treatment grades of oesophagitis (Lindberg et al., 2003).

Figure 4.2b shows the additional benefits of esomeprazole relative to the earlier PPIs.

**Figure 4.2b. Additional benefits of esomeprazole relative to the earlier PPIs**



*Sources: Adapted from: Andersson et al. (2000); Lind et al. (2000); Andersson et al. (2001); Richter et al. (2001b); Carlsson et al. (2002); Kahrilas et al. (2002); Lindberg et al. (2003)*

### **Antiepileptic drugs (AEDs)**

Epilepsy is among the most common of all the serious neurological disorders worldwide. It is estimated that 50 million people have epilepsy, and six million of these live in the EU (IBE, undated). The term epilepsy encompasses a wide variety of syndromes, rather than a homogeneous disease (for an overview see Berg et al., 2010). The cardinal feature of epilepsy is a predisposition to recurrent unprovoked seizures. Seizures are sudden, brief attacks of altered consciousness; motor, sensory, cognitive, psychic, or autonomic disturbances; or inappropriate behaviour caused by abnormal excessive or synchronous neuronal activity in the brain. Seizure semiology ranges from simple partial seizures, the consequences of which may only be noticeable by the individual, to more dramatic forms like generalised tonic-clonic (so called ‘grand mal’) seizures, to devastating forms like tonic and atonic seizures (‘drop attacks’), accompanied by a high risk for associated injuries, which can be found, for example, in Lennox-Gastaut syndrome, a catastrophic form of childhood-onset epilepsy (Arzimanoglou et al., 2009).

Antiepileptic drugs (AEDs) are a heterogeneous group of substances aiming at suppressing pathological neuronal activity resulting in epileptic seizures as a visible outer expression of this disorder. AEDs are able to prevent further seizures and reduce the severity of seizures, and treatment is recommended in all people with a high risk of seizure recurrence. Pragmatically, the choice of AED needs to be individualized based mainly on the patient profile, including the efficacy of the drug for different seizure types, tolerability, safety, ease of use, special requirements of polytherapy, comorbidities, and costs.

During combination therapy, a number of drug interactions may occur when classic AEDs are used, which may interfere with drug efficacy. As the majority of patients with epilepsy need AED for their lifetime, long-term consequences need to be taken into account. For example, women might wish to take oral contraceptives at some periods in life; people become overweight or develop comorbid conditions such as depression, anxiety disorders, migraine, cardiovascular disease, diabetes, and cancer, and may require additional medication to treat those problems. In addition, up to one in three patients with new-onset epilepsy require a combination of different AEDs for seizure control. Not uncommonly, three or more AEDs may be needed. The absence of drug-drug interactions is a very important advantage for an AED.

AEDs can be classified as 'first-generation', 'new-generation' or 'newest-generation' drugs. We now describe in turn the incremental benefits of these three classes of AEDs.

### **First-generation AEDs**

Drugs like carbamazepine and valproic acid, employed since the 1960s and 1970s for treating partial and generalised seizures, and still frequently used in current clinical practice, are often referred to as 'first-generation' AEDs. Although efficacious, they are pharmacologically problematic as: (1) they induce or inhibit the hepatic CYP450 system (which is involved in the metabolism of many drugs and endogenous substrates) with subsequent undesirable acute and long-term effects on therapeutic levels of co-administered drugs, and also on parameters like bone density and lipid profiles (for an overview, see Johannessen and Johannessen-Landmark, 2010); and (2) they exert an influence on enzymes involved in glucuronidation. Moreover, numerous adverse effects for first-generation AEDs have been described (Elger and Schmidt, 2008).

### **New-generation AEDs**

The so-called 'new-generation' AEDs with, for the most part, improved tolerability and pharmacological profiles (in particular, a reduced potential for drug-drug interactions (DDIs) and cognitive effects) and/or new mechanisms of action, like levetiracetam and lamotrigine, were introduced in the 1990s with a number of consequent benefits relative to first-generation AEDs (Elger and Schmidt, 2008). The UK SANAD trial (Marson et al., 2007), for example, showed that lamotrigine was superior to carbamazepine in terms of long-term effectiveness in the treatment of patients suffering from partial-onset seizures, based on a better tolerability. Moreover, health economic analysis additionally supported lamotrigine being preferred over carbamazepine for both cost per seizure avoided, and cost per quality-adjusted life year gained (Marson et al., 2007).

Of special importance is the antiepileptic treatment of elderly patients, in whom tolerability issues and avoidance of DDIs are a matter of special concern. First generation AEDs like phenytoin and carbamazepine are not attractive options for this age group, due to their enzyme-inducing properties and a high incidence of CNS-related side-effects. As noted by Elger and Schmidt (2008), experts generally recommend non-metabolised, non-enzyme-inducing, new AEDs such as gabapentin, lamotrigine, and levetiracetam, instead of classic enzyme-inducing AEDs such as carbamazepine, as preferable. Figure 4.3a illustrates the additional benefits of the new-generation AEDs.

**Figure 4.3a. Additional benefits of the new-generation AEDs relative to first-generation AEDs**



*Sources: Adapted from Marson et al. (2007) and Elger and Schmidt (2008)*

### Newest-generation AEDs

During the last few years a number of even newer AEDs have been marketed, such as lacosamide (EMA, 2008), eslicarbazepine acetate (EMA, 2009a; EMA, 2009b), and retigabine (EMA, 2011). These have been termed the ‘newest generation of AEDs’ (for an overview, see Perucca et al., 2007). All of these newest-generation AEDs are currently licensed as add-on therapy to other AEDs. The evidence provided in the European Medicines Agency (EMA) European Public Assessment Reports shows that they are effective in reducing the number of seizures for those patients with seizures that had not been controlled by other medicines.

These newest-generation AEDs drugs have been developed either by improving older substances, or by addressing new targets. For the former, the goal was to develop new drugs from substances proven to be efficacious against seizures, but with improved pharmacological properties as a result of modelling of the core chemical structure, and with expected advantages in clinical tolerability. This approach was followed for eslicarbazepine acetate, for example, which was developed from the first-generation AED carbamazepine.

The second approach is to develop AEDs which address new and potentially crucial targets involved in the generation and propagation of seizure activity. An example of this approach is retigabine, the first-in-class potassium-channel opener.

The additional benefits of new AEDs are important, as patients’ quality of life is negatively affected by stigmatising seizures as well as negative side-effects. Gilliam (2002) showed that the most decisive determinant for quality of life was the degree of medication side-effects experienced. As non-adherence to antiepileptic medication and resulting seizures is not only a major cause of increased

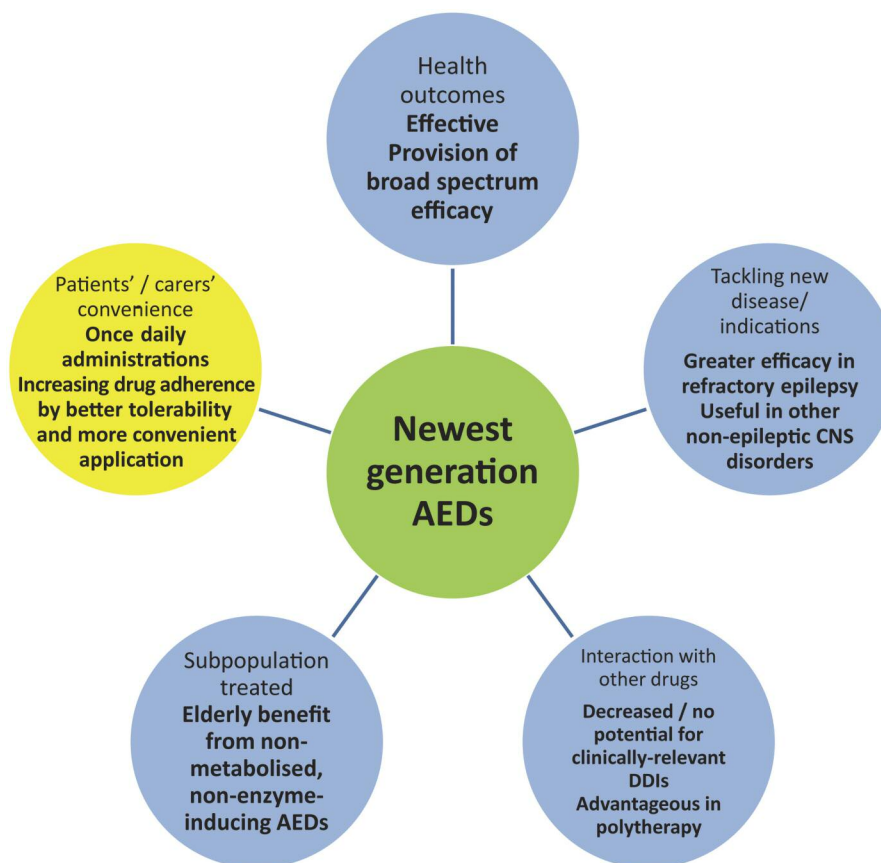
mortality associated with epilepsy (Faught et al., 2008) but also leads to increased healthcare utilisation costs (Faught et al., 2009), the aim of increasing AED adherence is a further important aspect for the development of new therapeutic options. By providing better tolerability, newer therapies promise to be easier to adhere to from a patient's perspective. Drugs developed to facilitate intake, for example by allowing once-daily administration, are of value as well. Making alternative application forms available, like syrup for paediatric or handicapped patients or intravenous formulations, are a field of particular importance in AED development.

With regard to patients with epilepsies labelled as pharmaco-resistant to standard therapies, more recent data indicate that, with the greater range of drug options having become available since the 1990s, the prognosis has improved. In a study by Luciano and Shorvon (2007), in which a systematic protocol for the addition or substitution of a formerly-unused AED (which 80 per cent of the time meant a 'newer-generation' AED) was applied in patients with epilepsies active for at least five years, it was shown that 28 per cent of patients could be rendered seizure free by the introduction of a new AED.

In addition to the potential benefits of new mechanisms of action in fighting established symptoms, one of the major goals for future research will be to address the unmet need for therapeutic agents that can prevent or at least delay the development of epilepsy by interfering with the process of epileptogenesis. Other goals will be the development of new substances with greater efficacy in refractory epilepsy than AEDs in current use; the provision of broad spectrum efficacy in different seizure forms; and usefulness in other, non-epileptic central nervous system (CNS) disorders (Bialer and White, 2010).

Figure 4.3b shows graphically the additional benefits of the newest-generation AEDs.

**Figure 4.3b. Additional benefits of the 'newest-generation' AEDs relative to earlier AEDs**



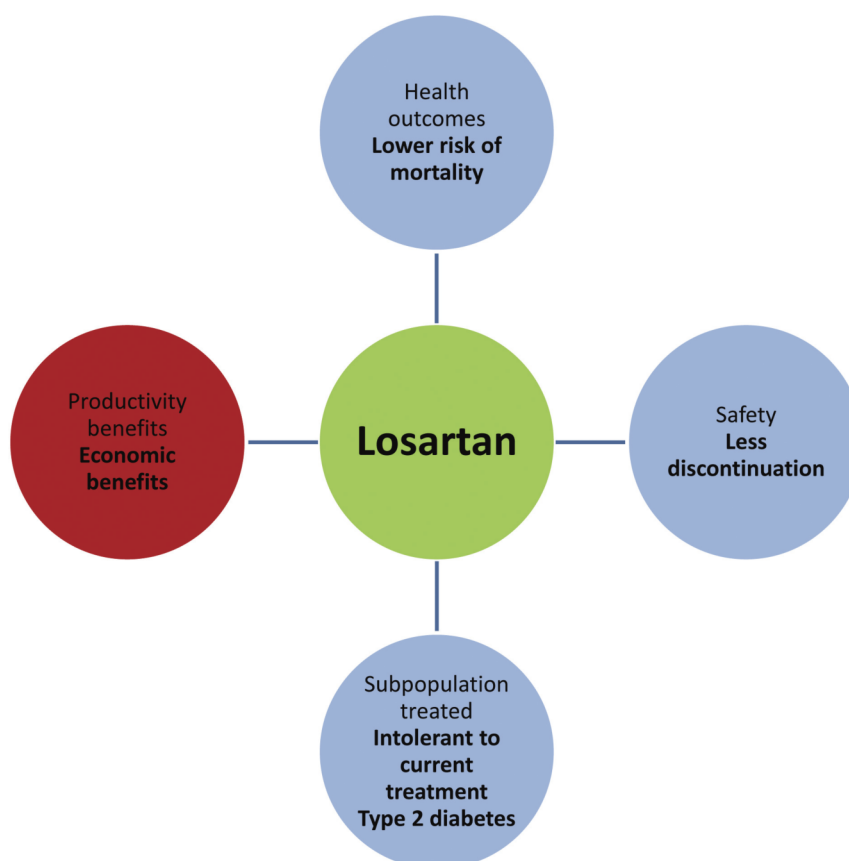
Sources: Adapted from Gilliam (2002); Luciano and Shorvon (2007); Faught et al. (2008, 2009)

### Chronic heart failure

The efficacy of angiotensin-converting enzyme (ACE) inhibitors is well documented in the treatment of chronic severe heart failure, by reducing mortality and hospitalisation. Given the different pharmacological mechanisms of angiotensin II type receptor antagonists (AIIA) relative to ACE inhibitors, an additional positive effect can be expected from combining these drugs (Gremmler et al., 2003).

Losartan was the first AIIA to be introduced. Relative to the most commonly-used ACE inhibitor, losartan was found significantly to reduce the risk of mortality and caused fewer adverse events leading to discontinuation (Desbach et al., 1999). Simpson and McClellan (2000) argue that losartan should be an option for first-line therapy in all patients with hypertension, particularly those not well managed by, or intolerant to, their current therapy. Jonsson et al. (2002) show that the improvements in cognitive function obtained with losartan, compared to an ACE inhibitor, leads to economic benefits beyond those expected in terms of blood pressure control among patients with hypertension. The addition of losartan to conventional antihypertensive therapy was found to reduce incidence of end-stage renal disease and to generate cost savings for patients with type 2 diabetes and nephropathy (Herman et al., 2003). Figure 4.4 shows these improvements schematically.

**Figure 4.4. Improvements relative to ACE inhibitors derived from the first AIIA**



*Sources: Adapted from Desbach et al. (1999); Simpson and McClellan (2000); Jonsson et al. (2002); Herman et al. (2003)*

Follow-on AIIAs have been introduced in the market, which can have additional benefits versus the first AIIA for particular groups of patients. For example, telmisartan has been found to reduce the time to hypertension control and costs relative to other commonly-prescribed therapies, for the treatment of patients with mild-to-moderate hypertension (Richter et al., 2001a). Irbesartan, another

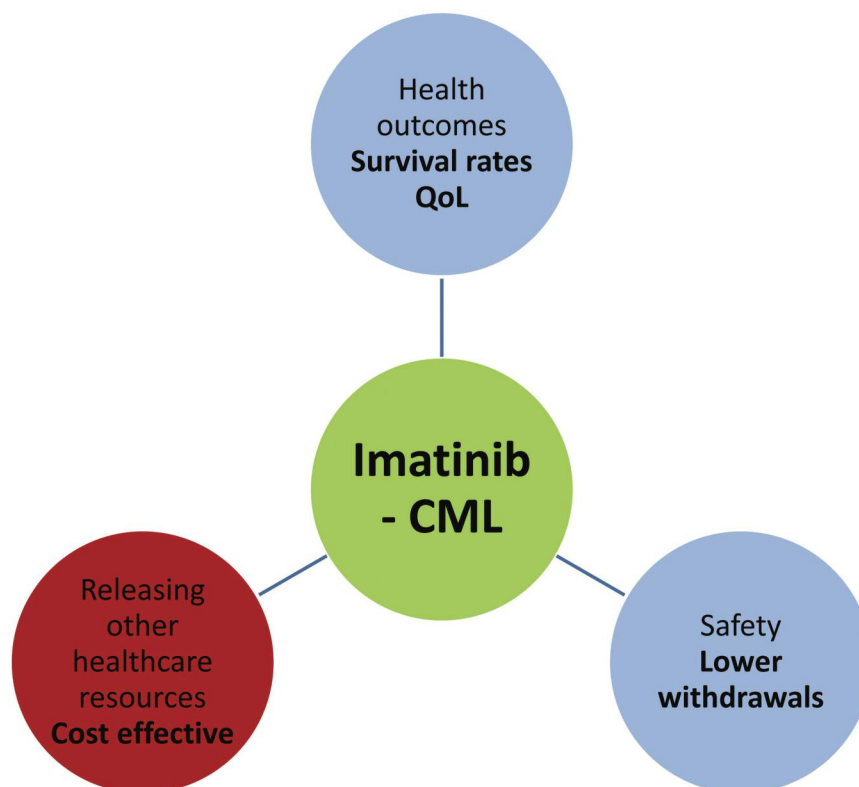
AIIA, delays the appearance of terminal renal insufficiency for type-2 diabetic patients, leading to higher quality of life, longer life and significant cost savings (Palmer et al., 2004). Croom et al. (2004) review the evidence on the use of irbesartan in hypertension and in the management of diabetic nephropathy. They find that irbesartan achieves a greater reduction in diastolic blood pressure and a greater or similar reduction in systolic blood pressure than losartan. They conclude that irbesartan is a well-tolerated and effective antihypertensive agent. Regarding hypertensive patients with type 2 diabetes, Croom et al. (2004) also show that irbesartan slows the progression of renal disease in this sub-population at both the early and later stages of diabetic nephropathy.

**Chronic myeloid leukaemia**

The only curative treatment for chronic myeloid leukaemia (CML) is stem cell transplantation. However, for a number of reasons, including shortage of donors and patient related-factors, this option is currently very limited. In recent years, the first-line treatment for those patients with no possibility of a stem cell transplant has been the alpha-interferons. When they were introduced they were considered to offer important medical gains in the treatment of some leukaemias, including CML, although they produce intolerable side-effects for around a quarter of people with CML (NICE, 2003a), including flu-like symptoms.

The introduction of imatinib, a tyrosine kinase inhibitor, has been an important discovery for the treatment of CML. The evidence analysed by NICE shows that imatinib is clinically and cost effective versus the previously-available best treatment. There are improvements in health outcomes, both in quantity (survival rates) and quality of life. Withdrawals because of side-effects are also less frequent with imatinib. Figure 4.5a shows the improved attributes as a result of imatinib compared with alpha-interferons for the treatment of newly-diagnosed CML patients.

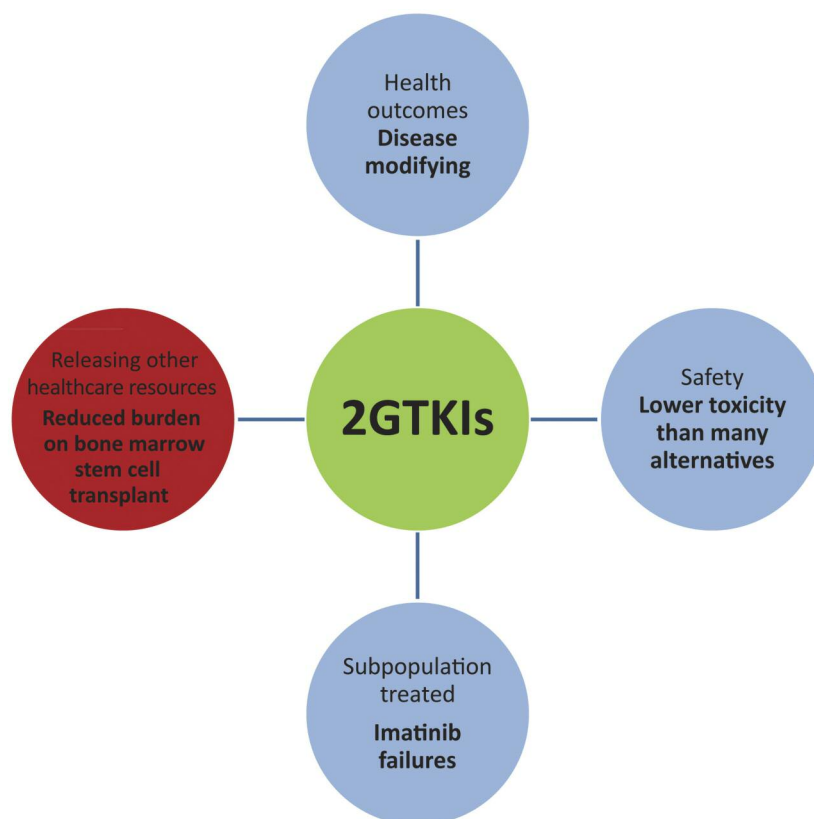
**Figure 4.5a. Imatinib – improvements relative to alpha-interferons for the treatment of newly-diagnosed CML patients**



*Source: Adapted from NICE (2003a)*

Despite the advance that has been demonstrated by imatinib in the management of CML, around 40 per cent of patients will fail therapy due to either imatinib resistance or intolerance (NICE, 2011). Since 2006 the introduction of the second-generation tyrosine kinase inhibitors (2GTKIs), dasatinib and nilotinib, has resulted in an important advance in the treatment of CML. Approximately 50 per cent of patients who fail to respond or tolerate imatinib will achieve treatment success with these agents (Shah et al., 2010; Kantarjian et al., 2011), which is a great improvement over the other treatment options available to such patients (including interferon-alfa, stem cell transplant, and best supportive care). At the time of writing, both dasatinib and nilotinib are the subject of an ongoing NICE appraisal in this setting. Figure 4.5b shows the improved attributes as a result of the 2GTKIs compared with the alternatives for patients who fail to respond to imatinib.

**Figure 4.5b. GTKIs – Improvements relative to standard of care for the treatment of imatinib-resistant/intolerant CML.**

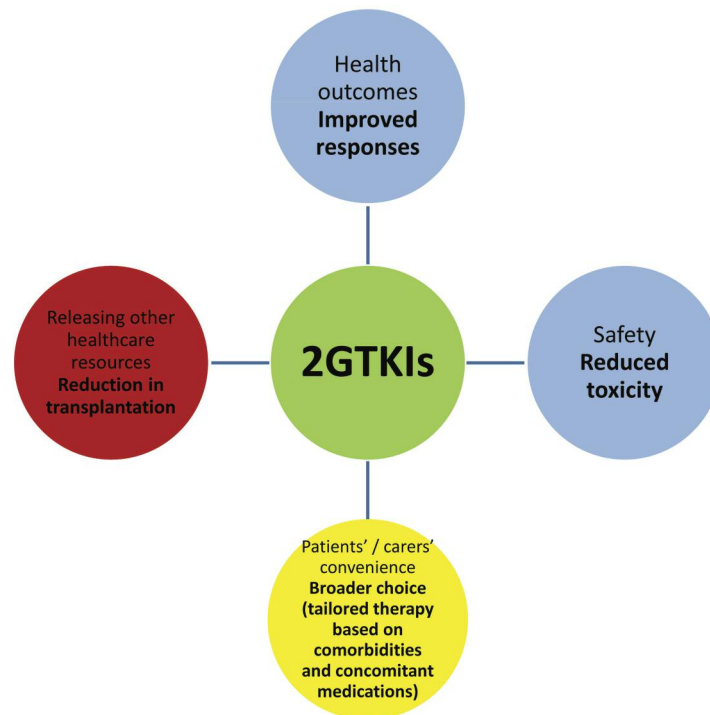


*Sources: Shah et al. (2010); Kantarjian et al. (2011)*

More recently, these 2GTKIs have been demonstrated to be more efficacious and less toxic than imatinib in newly-diagnosed CML patients (Kantarjian et al., 2010; Saglio et al., 2010), leading to key responses in a higher proportion of patients. These key responses have been shown to be surrogate markers for improvements in long-term outcomes (Hoyle et al., 2011). Again, both technologies are at the time of writing the subject of an ongoing NICE appraisal in this setting. Figure 4.5c shows the improved attributes as a result of the 2GTKIs relative to imatinib for newly-diagnosed CML patients.



Figure 4.5c. 2GTKIs – Improvement relative to imatinib for the treatment of newly-diagnosed CML



Sources: Kantarjian et al. (2010); Saglio et al. (2010); Hoyle et al. (2011)

### Colorectal cancer

Colorectal cancer (CRC) is one of the most common forms of cancer. It is often diagnosed late due to the absence of screening programmes, lack of knowledge about symptoms, and/or reluctance to seek medical help once the symptoms have appeared. Overall survival for CRC remains relatively poor (Kanavos and Schurer, 2010).

Colorectal cancer remained a therapeutic area in which medical treatment was considered to have little or no effect until the end of the 1980s. Chemotherapy is currently essential to provide a chance of cure for patients with more advanced disease and during the past 10 years a number of new agents have been introduced, with a subsequent increase in life expectancy from five to over 20 months (Kanavos and Schurer, 2010). Irinotecan and oxaliplatin appeared in the mid-1990s as treatments for both early and advanced colorectal cancer (Wilking et al., 2009). Capecitabine was then introduced for CRC in the early 2000s. More recently, two new drugs - bevacizumab and cetuximab - have been approved for the treatment of advanced colorectal cancer. Another drug, panitumumab, approved for a specific patient population, is the most recent introduction in this therapeutic area.

Before capecitabine was introduced, the standard treatment was 5-FU/FA. Capecitabine's main advantage is that it is an oral therapy, rather than having to be administered by infusion (as with 5-FU/FA). In addition to being more convenient for patients, there are potential costs savings that could be generated as a result of the method of administration and the reduced burden of preparation and administration on specialist staff (NICE, 2003b; SMC, 2008).

Irinotecan is licensed for use in chemotherapy-naive patients with advanced CRC in combination with 5FU/FA and also as a single agent for second-line chemotherapy in patients who have failed an established 5-FU based regimen. Median overall survival has been improved by the combination regimen by between 2.2 and 3.3 months, while median progression-free survival (PFS) has increased by between 2.1 and 2.7 months (NICE, 2005). Randomised clinical trials have shown that irinotecan in monotherapy in second line has improved median overall survival and median progression-free survival by 2.3 and 1.3 months respectively relative to second line 5-FU/FA.

Oxaliplatin in combination with 5-FU/FA is indicated for treatment of metastatic CRC. Results show that this combination increase the objective tumour response rate and extends median PFS by 2-3 months compared to 5-FU/FA alone, albeit with increased toxicity (NICE, 2005). The possibility of treating a subgroup of patients with metastases confined to the liver that may become resectable following surgery has been highlighted as a strong point of oxaliplatin as this treatment could provide significant survival gains for this segment of patients (NICE, 2005). As argued by NICE, given the different side-effect profiles of the medicines, having a range of drug treatment options available is deemed important. Figure 4.6a shows schematically the benefits derived from capecitabine, irinotecan and oxaliplatin relative to 5-FU/FA.

**Figure 4.6a. Benefits derived from capecitabine, irinotecan and oxaliplatin relative to 5-FU/FA for the treatment of colorectal cancer.**



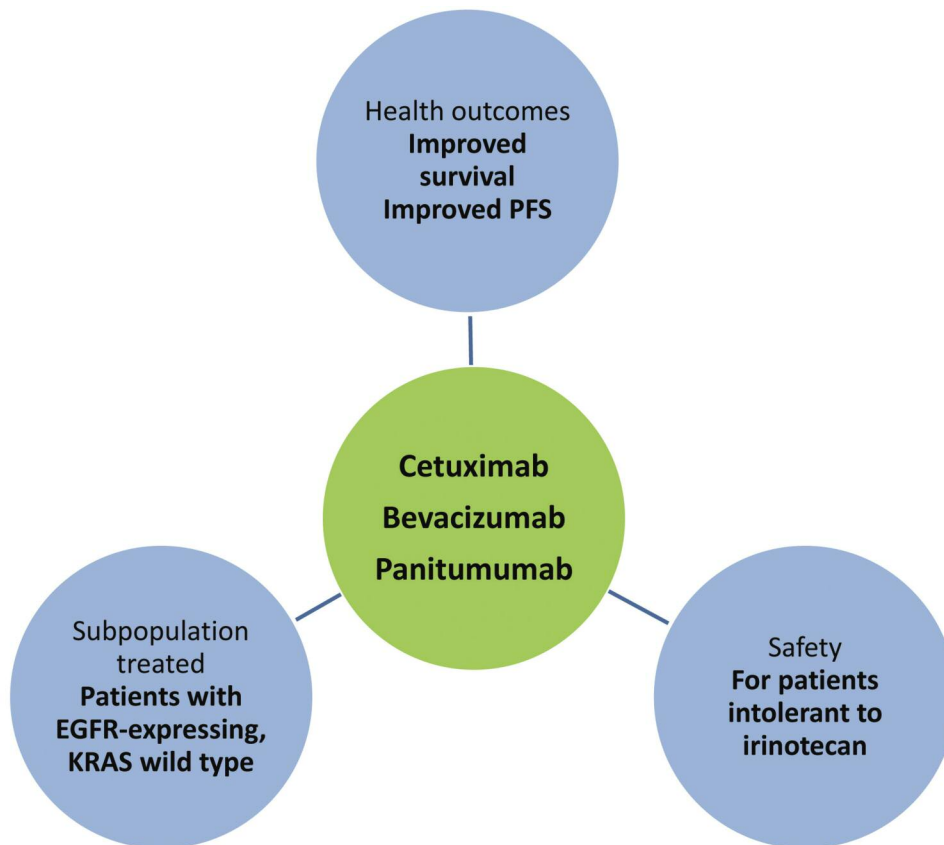
*Sources: Adapted from NICE (2003b; 2005); SMC (2008)*

There are now even newer, biotech drugs to treat colorectal cancer: cetuximab, bevacizumab and panitumumab. These have benefits for a specific sub-population. In particular, cetuximab is indicated for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer, in combination with chemotherapy as well as indicated for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer, as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

When looking only at the KRAS wild-type, median progression-free survival and overall survival were higher for those patients receiving the combination regimen including cetuximab, (NICE, 2007; 2009b). Also, cetuximab combined with chemotherapy has an important potential role in shrinking secondary liver metastases, to enable potentially curative resection in people with KRAS wild-type metastatic colorectal cancer (NICE, 2007; 2009b).

Figure 4.6b illustrates the additional benefits from cetuximab, bevacizumab and panitumumab for the treatment of colorectal cancer.

**Figure 4.6b. Additional benefits from cetuximab, bevacizumab and panitumumab relative to previous treatments, for colorectal cancer**



*Sources: Adapted from NICE (2007; 2009b)*

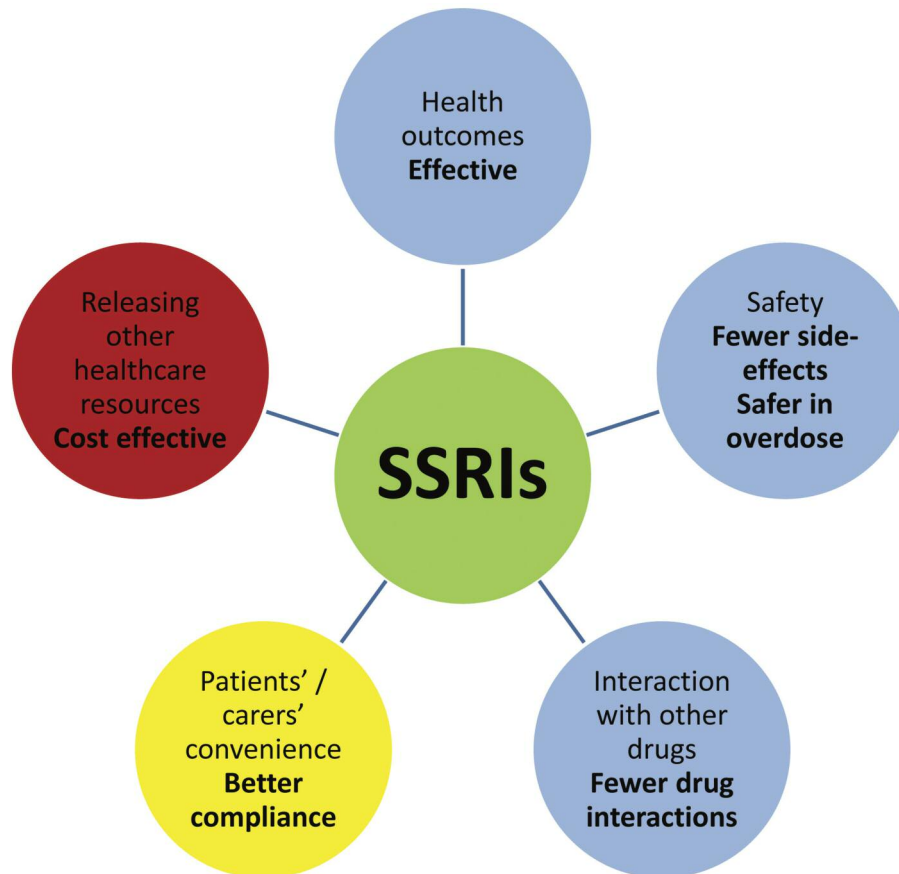
### **Depression**

Depression is a common, life-disrupting, potentially lethal illness that can affect both sexes and all ages. Although the causes of depression are not completely known, a range of effective antidepressants is available and is widely used by psychiatrists to treat various subtypes of depression. Fluoxetine was the first of a group of antidepressant agents known as selective serotonin reuptake inhibitors (SSRIs), which were developed in the late 1980s and are currently the first-line pharmacotherapy for depression. The SSRI group includes fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram oxalate.

Clinical evidence shows SSRIs to be as effective as traditional tricyclic antidepressants (TCAs), but with fewer safety and tolerability problems. The improved side-effect profile is reflected in the better compliance seen even in the controlled studies. In addition, SSRIs have fewer drug interactions than traditional antidepressants, they are more suitable for use in long-term maintenance therapy, and are associated with fewer deaths from overdosage (Mourilhe et al., 1998; Montgomery, 2000; Cipriani et al., 2003).

In a review of the economics literature comparing SSRIs in general and TCAs, Stewart (1998) found that almost all studies combining clinical outcomes with a full range of healthcare costs suggest that SSRIs are cost effective. In particular, Stokes and Holtz (1997) highlight that fluoxetine can reduce healthcare costs by ‘reducing the need of physician contact because of increased compliance, by reducing premature patient discontinuation, thereby yielding fewer relapses, less recurrence, and less reutilisation of mental health services’. Figure 4.7 illustrates the additional advantages derived from the SSRIs relative to TCAs.

Figure 4.7. Additional benefits of SSRIs versus TCAs for the treatment of depression



Sources: Adapted from Stokes and Holtz (1997); Mourilhe et al. (1998); Stewart (1998); Montgomery (2000); Cipriani et al. (2003)

Pharmacological considerations suggest that SSRIs are a heterogeneous class (Cipriani et al., 2003). There are differences in both their primary pharmacological action (ie selective and potential inhibition of serotonin reuptake) and their secondary action (blockade of norepinephrine and dopamine reuptake). A systematic review of head-to-head studies shows no difference in efficacy between individual compounds but highlights some difference in tolerability (Edwards and Anderson, 1999).

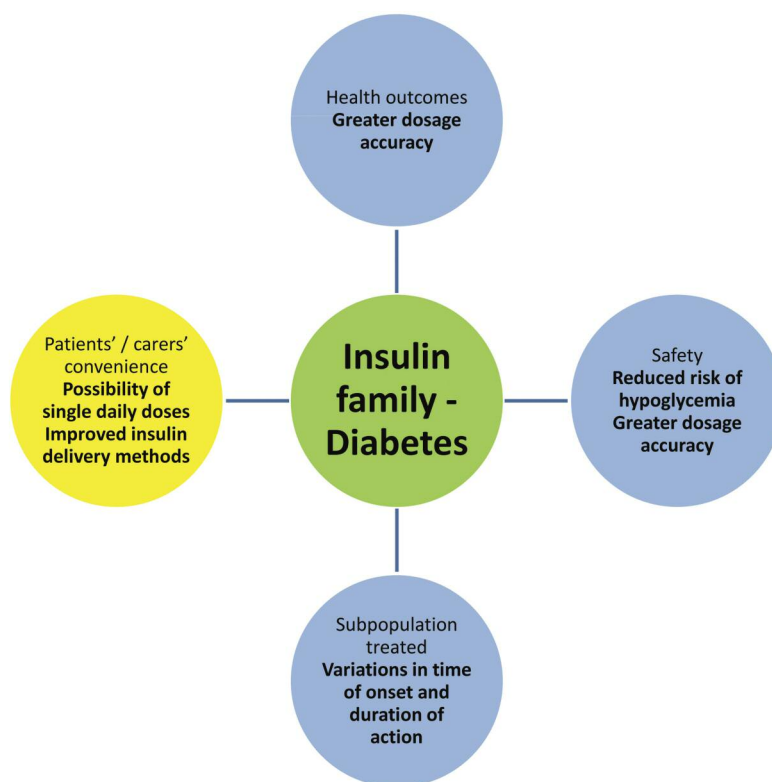
As with all antidepressant therapies, there is variability among very depressed patients in terms of response to SSRI treatment: about 30-40 per cent of them do not respond sufficiently to SSRIs. However, it has been found that patients who fail to respond to one drug can respond to another agent of the same class (Wertheimer et al., 2001). One study has highlighted that 26 per cent of non-responders to fluoxetine did respond to sertraline (Zarate et al., 1996). Another study has shown that 63 per cent of non-responders to sertraline did respond to fluoxetine (Thase et al., 1997). More generally, it has been suggested that switching from one SSRI to another has an overall success rate of 51 per cent (Joffe et al., 1996). Regarding differences in economic evaluation among individual SSRIs, a more recent review by Croom and Plosker (2003) found that escitalopram may be a cost-effective alternative to generic citalopram, generic fluoxetine and sertraline.

The availability of a broad range of medicines within the class of SSRIs has also increased the competition on price among these agents. DiMasi (2000) has reported that fluvoxamine and citalopram (follow-on products) were launched at price discounts relative to the class price leader and not just to the average price in the class.

## Diabetes

The insulin molecule has been extensively manipulated to provide a range of insulin products for the treatment of diabetes. Insulin products have been available since the 1970s, and there have been technical improvements over the decades in terms of added patients' convenience, improved compliance, greater dosage accuracy, and reduced side-effects, including reduced risk of hypoglycaemia (Wertheimer et al., 2001). In addition, there have been improvements in insulin delivery methods, including pen-type multiple dose injection services. There is currently research in progress to develop insulin nasal sprays, which, if successful, would eliminate the need for meal-time injections for some patients (ABPI, 1999). This delivery method has the obvious potential to, among other things, improve patients' convenience. Figure 4.8a shows how the wide range of insulin products affects positively some of the different dimensions of innovation from Figure 3.1.

Figure 4.8a. Insulin treatments for diabetes



Source: Adapted from Wertheimer et al. (2001)

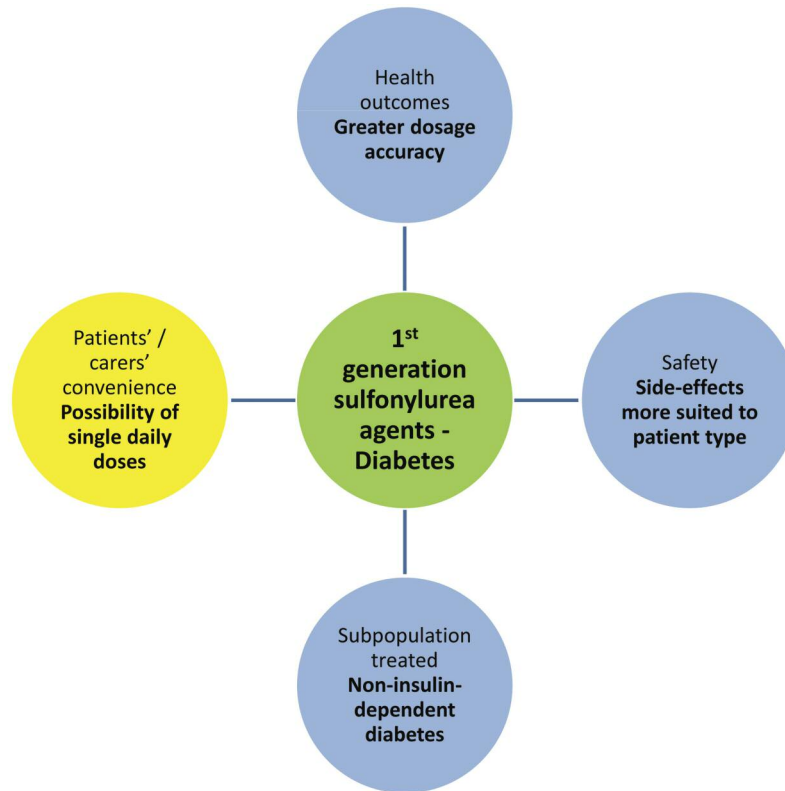
## Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is traditionally characterised by insulin resistance and  $\beta$ -cell dysfunction, leading to hyperglycaemia and eventual micro- and macro-vascular complications if not adequately managed (Campbell and Neumiller, 2010). Diabetes care is complex and time-consuming as it involves lifestyle changes, and managing the side-effects of therapy with patient monitoring and education (NICE, 2009a).

Treatments for patients of non-insulin-dependent diabetes are also available: oral glucose-lowering drugs. By 2000 there were two possibilities for the use of these treatments: monotherapy (either taking metformin or a sulfonylurea) or combination therapy (taking both together). The efficacy of combination therapy became established in the 1980s for those patients whose diabetes was not controlled by monotherapy, a decade after metformin and the first-generation sulfonylureas were made available. Combination therapy increased therapeutic options and allowed better management of diabetes (NERA, 2004).

There are several first-generation sulfonylureas available. Although of similar molecular structure, they differ in potency, duration of action, dose range and side-effects (Wertheimer et al., 2001). This variation implies that each agent will better suit different groups of patients according to their nutritional status and dietary habits, age, and other medical conditions. The benefits derived as a result of the multiple first-generation sulfonylurea agents are shown in Figure 4.8b.

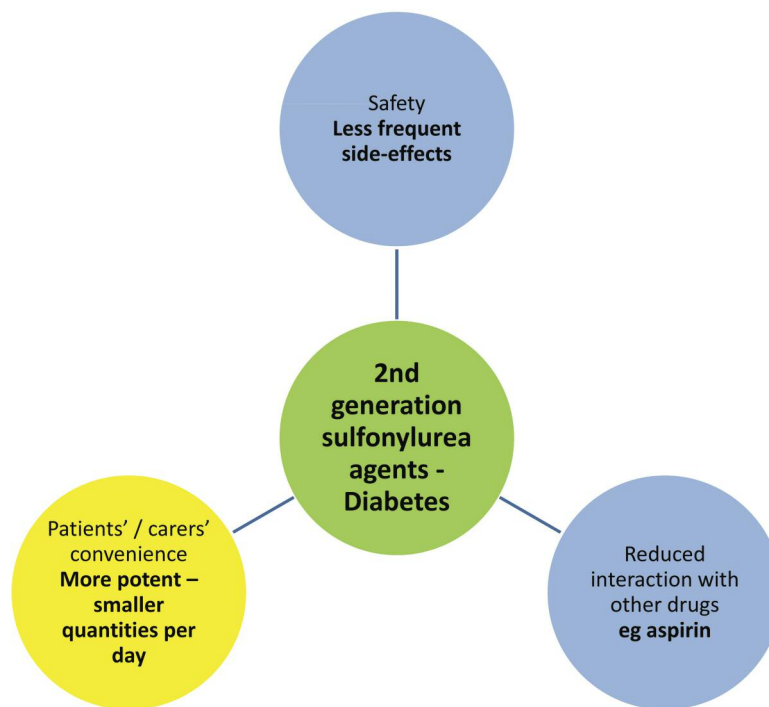
**Figure 4.8b. Benefits derived from first-generation sulfonylurea agents**



*Source: Adapted from Wertheimer et al. (2001)*

In the 1980s, second-generation sulfonylureas were approved. Again, there are several, with similar molecular structures but differences in potency, duration of action, dose range, side-effects and convenience. Second-generation sulfonylurea agents are more potent than first-generation agents, with the convenience that smaller quantities per day need to be taken. Side-effects occur less frequently and there is reduced potential for negative interaction with aspirin (Wertheimer et al., 2001). The advances due to second-generation versus first-generation sulfonylurea agents are shown in Figure 4.8c.

**Figure 4.8c. Benefits derived from second-generation sulfonylurea agents relative to first-generation agents**



*Source: Adapted from Wertheimer et al. (2001)*

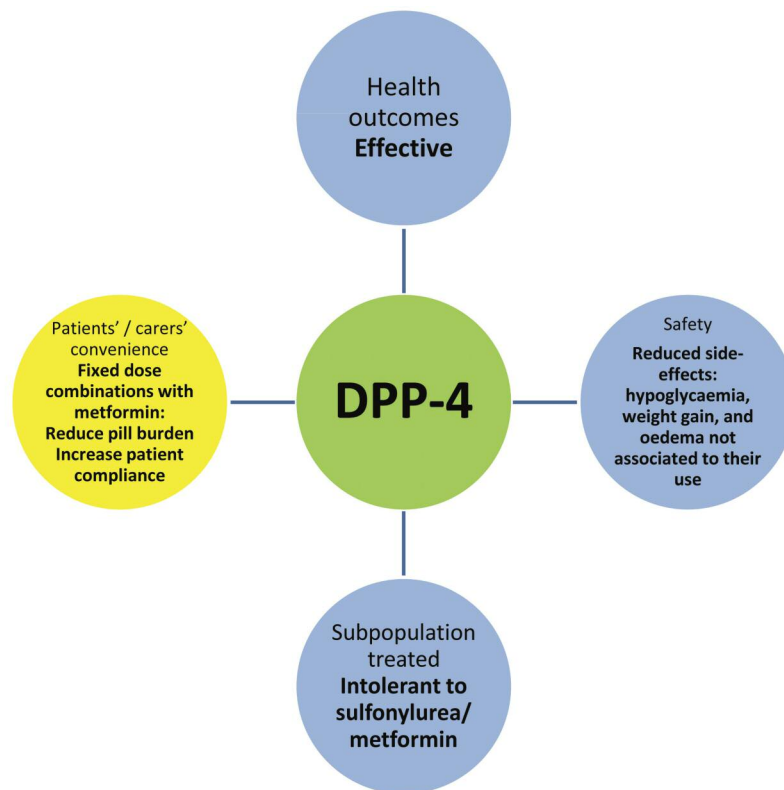
Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of drugs available for the management of T2DM. In 2006, the US Food and Drugs Administration (FDA) approved the first in class DPP-4 inhibitor, sitagliptin. DPP-4 inhibitors increase circulating concentrations of incretin gastrointestinal hormones (GLP-1 and glucose-dependent insulinotropic polypeptide-1). Incretins are rapidly released after meals, and they stimulate glucose-dependent insulin secretion. DPP-4 inhibitors improve glycaemic control by blocking the effect of dipeptidyl peptidase-4, which is responsible for the rapid inactivation of incretins, mainly GLP-1 (Charpentier et al, 2010).

DPP-4 inhibitors offer a new mechanism of action, which is complementary to that of metformin (Charpentier et al, 2010). NICE guidelines (2009a) consider adding DPP-4 inhibitors in combination treatment or as monotherapy.

Given that the diabetes treatment paradigm is an add-on one, fixed dose combinations are becoming important to reduce the pill burden and increase patient compliance. Examples are: Januvamet (50mg sitagliptin and 500 or 1000mg of metformin twice daily), Kombiglyze XR (5mg saxagliptin and up to 2000mg of metformin once daily). Further, hypoglycaemia, weight gain and oedema are generally not associated with DPP-4 inhibitor therapy (Charpentier et al, 2010).

Since the approval of sitagliptin in 2006, other DPP-4 inhibitors have been approved. Campbell and Neumiller (2010) provide a comprehensive evaluation and comparison of the pharmacology, pharmacokinetics, efficacy and safety of four DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin and alogliptin. Based on information from preclinical, clinical and post-marketing data, they argue that there does not appear to be a compelling advantage of one DPP-4 inhibitor over another in terms of efficacy, safety, or ease of clinical use. However, further comparative studies and/or increased clinical experience are needed to determine whether in practice the different DPP-4 inhibitors have any advantages relative to each other, eg for particular patient subgroups. Figure 4.8d shows the additional benefits of DPP-4 inhibitors for the treatment of T2DM, as a group, relative to the previously available treatments.

**Figure 4.8d. Additional benefits of DPP-4 inhibitors for the treatment of T2DM, relative to previous treatments**



Sources: Adapted from NICE (2009a); Charpentier et al. (2010)

### ***Granulocyte colony-stimulating factor (G-CSF)***

Chemotherapy is one of the mainstays in the treatment of cancer and can be used either in a curative or palliative setting. However, along with the benefits, chemotherapy is associated with a wide range of treatment-related toxicities. Chemotherapy-induced neutropenia (CIN), the most serious haematologic toxicity, can lead to febrile neutropenia (FN). FN is an emergency complication associated with a high mortality rate and negative impact on effective chemotherapy delivery (Aapro et al., 2011). The management of FN has a substantial economic burden, emergency admissions, increased bed days, and increased capacity demands on hospital and community nurse resources.

Filgrastim, the first granulocyte colony-stimulating factor (G-CSF) and among the first 'biotech' products developed, has revolutionised cancer treatment with cytotoxic chemotherapy by reducing the incidence of FN, FN-related hospitalisations and infections (Renwick et al., 2009). Filgrastim and other supportive care products have allowed the intensification of chemotherapy (dose-dense or dose-intensive regimens) up to high-dose therapy that requires stem cell transplantation (Aapro et al., 2011). Improved chemotherapy strategy through elimination of dose-limiting neutropenia has resulted in better survival (Aapro et al., 2011, Renwick et al., 2009) in several solid tumours and hematological malignancies where the cancer cells are sensitive to chemotherapy (eg AML, NHL, breast cancer) and where chemotherapy is often the only curative option.

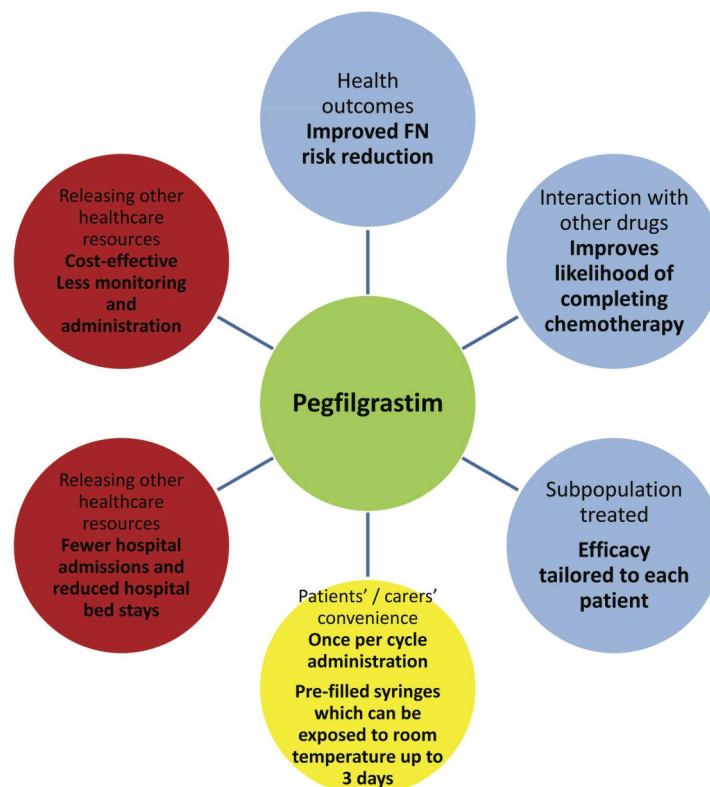
Filgrastim is administered via daily injections through a chemotherapy course and is quickly eliminated from the body (Neupogen SPC, 2011). Dosing is based on patient bodyweight and neutrophil count is monitored by the physician. Furthermore, Filgrastim is a protein, with the consequence that syringes should be kept in a refrigerator between 2-8 °C (Neupogen SPC, 2011), requiring maintenance of cold chain distribution from wholesaler through the pharmacy to the patient's home.



Pegfilgrastim has been developed by adding a polyethylene glycol (PEG) moiety to filgrastim. This process changes its route of elimination, making clearance of pegfilgrastim ‘self-regulated’ (Neulasta SPC, 2011). Pegfilgrastim remains in the plasma of the patients until its effect is required and is eliminated once the blood count is normalised - the efficacy is tailored to the needs of each patient. Due to its long-lasting effect, Pegfilgrastim is administered only once per chemotherapy cycle with a fixed dose, irrespective of the bodyweight of patients (Neulasta SPC, 2011). This offers benefits for both patients and staff (SMC, 2003a). Pegfilgrastim is more effective in reducing the incidence of FN compared with daily G-CSFs (Von Minckwitz et al. (2008), Almenar et al. (2009)) and is also cost effective compared with current practice daily G-CSFs in many European countries (Whyte et al., 2011). It leads to lower overall expenditure on FN management through fewer hospital admissions and bed days, and reduced healthcare professional resource and capacity in delivery (single injection vs. multiple injections). Pegfilgrastim is marketed as a pre-filled syringe, with recent introduction of an automatic needle guard, and can be exposed to room temperature for up to three days rather than needing to be refrigerated (Neulasta SPC, 2011).

Figure 4.9 highlights the benefits related to the use of pegfilgrastim in chemotherapy. The innovation in both biology and pharmaceutical form have allowed patients to be treated at home with a more efficacious product, receiving an injection only once per chemotherapy cycle and significantly reducing monitoring of treatment effect.

**Figure 4.9. Benefits related to the use of pegfilgrastim in chemotherapy**

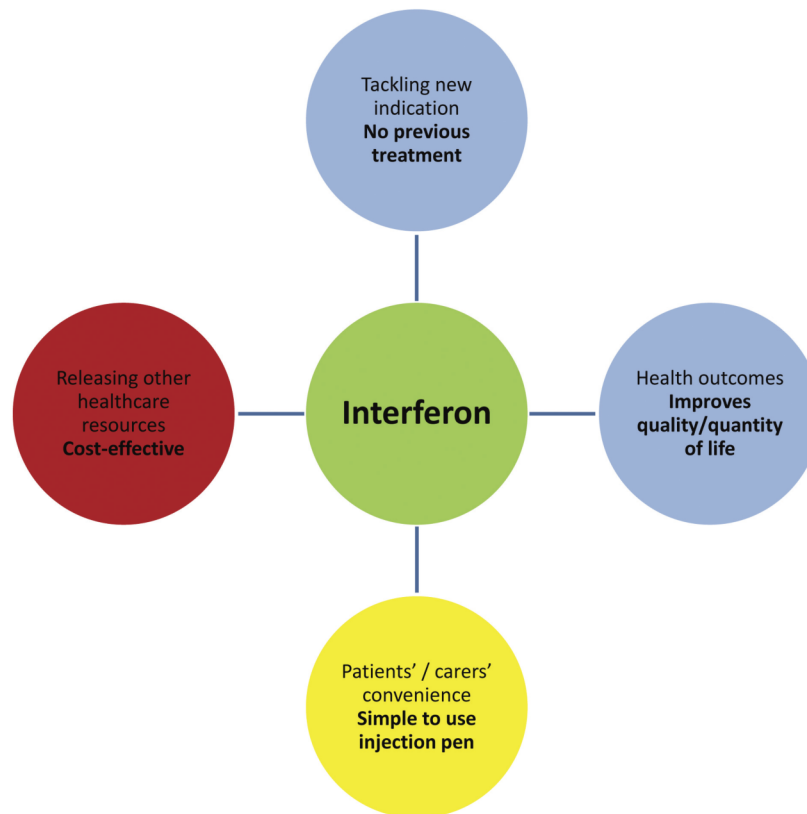


*Sources: Adapted from Von Minckwitz et al. (2008); Almenar et al. (2009); Neulasta SPC (2011); Whyte et al. (2011)*

## Hepatitis C

There is currently no vaccine for Hepatitis C. Until recently, the only approved treatment was interferon alpha, which is considered to be efficacious given that in 25 per cent of cases it prevents the virus from multiplying and eradicates the disease altogether. In other cases, the disease may replicate. Interferon alpha also improves several quality of life measures, although side-effects exist. In particular, it is hard to tolerate for many (although not all) people and drop-out rates have been estimated to be around 7-14 per cent. Figure 4.10a shows the benefits of interferon alpha schematically.

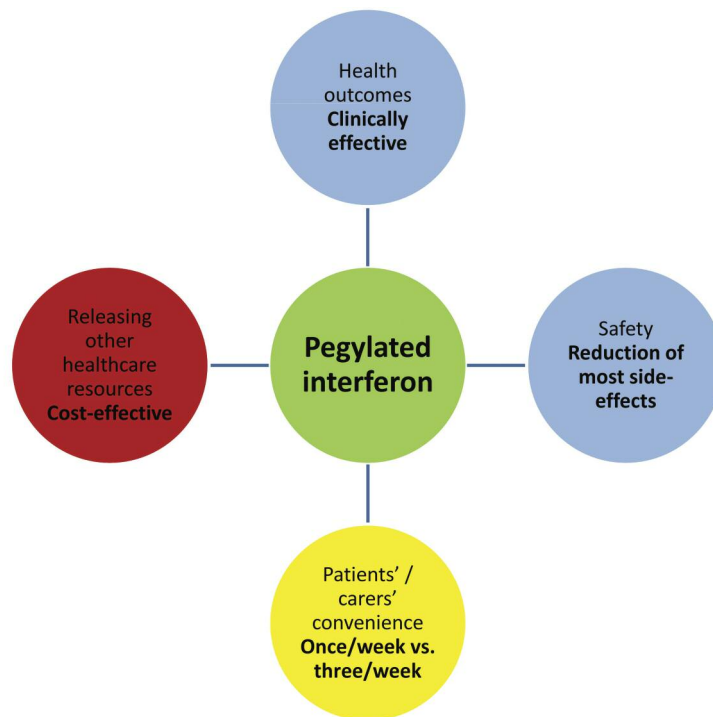
Figure 4.10a. Benefits from interferon alpha for the treatment of Hepatitis C



Sources: Adapted from ABPI (1998); NICE (2004)

Recently a new type of interferon alpha has been introduced – the pegylated interferon. In the early 2000s, two product licences have been granted for pegylated interferon for the treatment of Hepatitis C. Figure 4.10b shows the additional benefits derived from this relative to the earlier interferon alpha.

**Figure 4.10b. Additional benefits derived from pegylated interferon, relative to interferon alpha, for the treatment of Hepatitis C**



*Sources: Adapted from ABPI (1998); NICE (2004)*

Evidence provided by the UK's National Institute for Health and Clinical Excellence (NICE) shows that pegylated interferon is both clinically and cost effective compared with interferon alpha (NICE, 2004). Hence, while interferon alpha provided the first treatment for Hepatitis C, pegylated interferon offers benefits as a result of improved health gains, including reducing most side-effects, improved patients' convenience, and cost savings. Figure 4.10b illustrates this schematically, highlighting just those dimensions of innovation (shown in Figure 3.1 earlier) where pegylated interferon is most clearly differentiated from interferon alpha.

### **HIV**

Over the last 30 years there has been a paradigm shift in the impact of clinical management on the natural history of HIV disease, which has been transformed from a uniformly fatal infection resulting in an undignified death, to a manageable chronic disease. This has been realised predominantly through greater understanding of the disease process, linking viral replication to immune dysregulation and destruction of CD4 cells, resulting in disease progression and susceptibility to opportunistic infections. Such understanding has formed the foundation for innovative targeted drug development that seeks to control viral replication. As a result of antiretroviral drug therapy, survival of infected patients has increased considerably from the matter of months or a few years that it was in the early 1980s, when the manifestations of HIV infection as an unusual immune deficiency syndromes among young homosexual males in New York and San Francisco was first recognised (later characterised as AIDS), to the current near-normal life expectancy of infected individuals, once treatment is accessible and diagnosis is made early enough. As antiretroviral therapy (ART) has evolved, combination therapies with multiple drugs have become the standard of care.

The first drug approved for the treatment of HIV/AIDS was the nucleoside reverse transcriptase inhibitor (NRTI or nucleoside analogue) zidovudine (AZT, Retrovir<sup>®</sup>), licensed in the UK in 1987 (Retrovir<sup>®</sup>, 2011). Other NRTIs soon became available. However, it was recognised that the effect of monotherapy was brief and limited in its activity against HIV (Concorde Coordinating Committee,

1994). With the advent of double combination nucleoside analogue therapy, greater drops in plasma HIV RNA were possible and there were some improvements in CD4 cell counts. The DELTA trial confirmed that HIV therapy with two NRTIs was superior to monotherapy (Delta Coordinating Committee, 1996). Regimens using just two NRTIs, however, did not provide a durable effect. Adding a third NRTI to create a triple combination did not improve long-term efficacy either (Gulick et al., 2004).

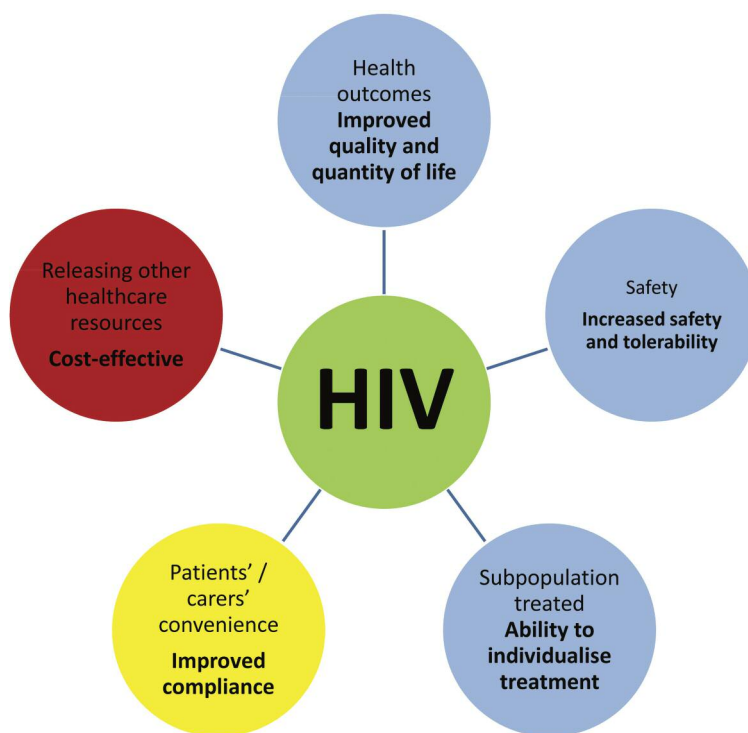
Protease inhibitors (PIs) were an important addition to HIV therapy. The first PI, saquinavir (SQV, Invirase®) appeared in 1996 (Invirase®, 2011). Several other PIs have subsequently become licensed. The efficacy of AZT+lamivudine (3TC) in combination with indinavir (IDV) was compared to AZT+3TC and IDV monotherapy. Huge media coverage followed the results as PIs were thought to be the cure for AIDS. The combination of AZT+3TC+IDV provided potent viral suppression through three years of follow-up (Gulick et al., 2000).

The introduction of non-nucleoside reverse transcriptase inhibitors (NNRTIs) came in 1998 with the approval of nevirapine (NVP, Viramune®), followed by efavirenz (EFV, Sustiva®) in 1999 (Viramune®, 2011; Sustiva®, July 2011). The first study investigating the use of two NRTIs and either a NNRTI or a PI, was DMP 266-066. Over three years, there is a superior durable response with EFV+AZT+3TC compared to IDV+AZT+3TC (Tashima et al., 2004).

This evolution led to the combination of two NRTIs with a PI or an NNRTI, known as HAART, becoming the gold standard of treatment, recommended by several national and international guidelines (European AIDS Clinical Society (EACS), 2011; Gazzard, 2008; Department of Health and Human Services, 2011; Thompson et al., 2010). Following HAART, HIV treatment is continuing to evolve. Current HIV therapies have demonstrated survival benefits but require life-long commitment from the patient and can lead to complications such as metabolic disorders, gastrointestinal, renal, cardiac, hepatic side-effects and resistance. New generations and classes of antiretroviral agents are currently in development.

Figure 4.11 shows the benefits derived from the increased availability of treatments for HIV.

**Figure 4.11. Benefits derived from the increased availability of treatments for HIV**



Sources: Delta Coordinating Committee (1996); Gulick et al. (2000); Tashima et al. (2004)

### ***Lipid lowering drugs: statins***

Cardiovascular disease (CVD) is defined as disease of the heart and blood vessels. The most common manifestation of CVD is coronary heart disease (CHD), also known as coronary artery disease and ischaemic heart disease. CVD predominantly affects people older than 50 and age is the main determinant of risk. Apart from age and sex, three modifiable risk factors – smoking, raised blood pressure and raised cholesterol – make major contributions to CVD risk, particularly in combination. In particular, blood cholesterol has a log-linear relationship to the risk of CHD and is a key modifiable risk factor (NICE, 2010).

CVD is the single most common cause of death in the UK; in 2005, CVD was the cause of one in three deaths (NICE, 2010). Despite the reduction in CVD since the 1970s and 1980s, it still remains a leading cause of death, in particular of premature death; an increasing cause of morbidity; and a major cause of disability and ill-health (NICE, 2010). CHD has been estimated to be the leading cause of disability in Europe, accounting for 9.7 per cent of total disability-adjusted life years (NICE, 2006).

Earlier treatments available to lower plasma lipids had been shown to reduce complications of CHD, but not overall mortality (Oliver et al., 1978). The introduction of statins was a major therapeutic advance (Sheridan and Attridge, 2006). Statins have been shown to reduce cholesterol levels – and it has been proven that interventions that lower LDL cholesterol concentrations can significantly reduce the incidence of CHD and other major vascular events in a wide range of individuals (Baigent et al., 2005). Therapy with a statin has been associated with a statistically significant reduction in risk of all-cause mortality, cardiovascular mortality, CHD mortality and fatal MI (Baigent et al., 2005). There is also evidence about the positive effects of statin use on non-fatal outcomes: as stated by Baigent et al. (2005), these findings reinforce the need to consider prolonged statin treatment with substantial LDL cholesterol reductions in all patients at high risk of any type of major vascular event.

Statins were first approved for secondary prevention of CVD, ie for patients with established CVD. The shift from use in secondary prevention to primary prevention (to prevent cardiovascular events in people who have no clinical evidence of CVD) was also hugely important. The first approval in primary prevention was pravastatin, based on evidence from the WOSCOPS study (Shepherd et al., 1995; Ford et al., 2007).

A number of statins have become available since the first one launched in 1987 (lovastatin). Subsequently, simvastatin was launched in 1988, pravastatin in 1990, atorvastatin in 1997 and rosuvastatin in 2003 (Sheridan and Attridge, 2006). Overall, atorvastatin and rosuvastatin are the most potent statins with respect to lowering LDL, followed by simvastatin and pravastatin (Hulisz, 2007).

Lovastatin, pravastatin, and fluvastatin represent the class members with the lowest potency but are attractive candidates for use in patients who have proven intolerant of more potent statins such as atorvastatin, simvastatin, or rosuvastatin (Kapur and Musunuru, 2008).

Atorvastatin and simvastatin have significantly improved efficacy in reducing LDL-C levels compared to the earlier statins. The benefits of simvastatin have been well documented (4S, 1994) and it has shown to be a more effective medicine than pravastatin (for instance, Sasaki et al., 1997). Subsequently, atorvastatin has produced greater reductions in total cholesterol than simvastatin, pravastatin, lovastatin and fluvastatin (Jones et al., 1998). If drug development had stopped at the first or second statin, additional benefits would have been missed.

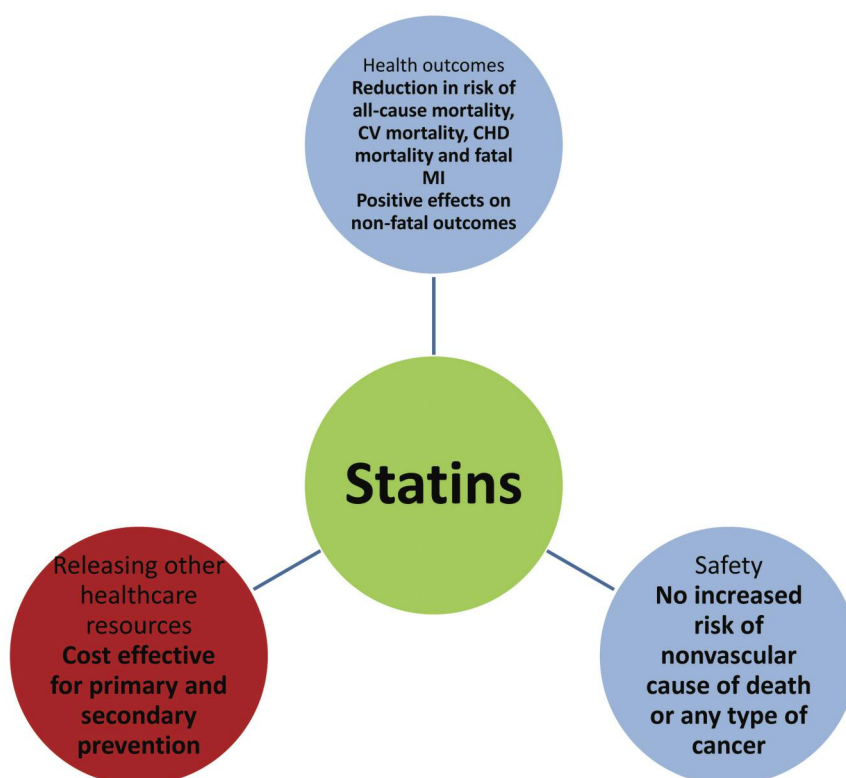
Rosuvastatin, the last statin made available, reduces total cholesterol significantly more than simvastatin and pravastatin (Jones et al. 2003). Rosuvastatin was also more efficacious in improving the lipid profile of patients with hypercholesterolemia than atorvastatin, simvastatin and pravastatin (Jones et al., 2004). Subsequently, in clinical practice, rosuvastatin was more effective and cost effective in lowering LDL-C and in attainment of ATP III LDL-C goals compared with atorvastatin or simvastatin among high-risk patients (Ohsfeldt et al., 2006).

Statins have been used widely and safely, and data on the effects of statins is one of the largest of any therapeutic area. Baigent et al. (2005) showed there was no evidence that lowering LDL cholesterol with five years of statin therapy increased the risks of any specific non-vascular cause of death or of any specific type of cancer.

NICE has recommended the use of statins for both primary and secondary prevention of CVD (NICE, 2006; 2010). The Scottish Medicines Consortium (SMC) has also deemed rosuvastatin and atorvastatin as cost-effective treatments (SMC, 2003b; 2005). Statins have always been cost effective and are now becoming cheap (as the earlier statins are coming off-patent), allowing wide population deployment.

Figure 4.12 shows the benefits of the statins as a class.

**Figure 4.12 Benefits of the use of statins for CVD**



Sources: Adapted from 4S (1994); Sasaki et al. (1997); Jones et al. (1998; 2003; 2004); SMC (2003b; 2005); Baigent et al. (2005); NICE (2006; 2010); Ohsfeldt et al. (2006); Hulisz (2007); Kapur and Musunuru (2008)

### **Thrombolytics**

The first thrombolytic agent to treat acute myocardial infarction (AMI) was streptokinase. This agent was an important evolution in the treatment of AMI. However, streptokinase can only be used once because people using it develop antibodies in their blood preventing streptokinase from working if treated with it again. Newer thrombolytic agents have recently been introduced, with the significant advantage that they can be used more than once.

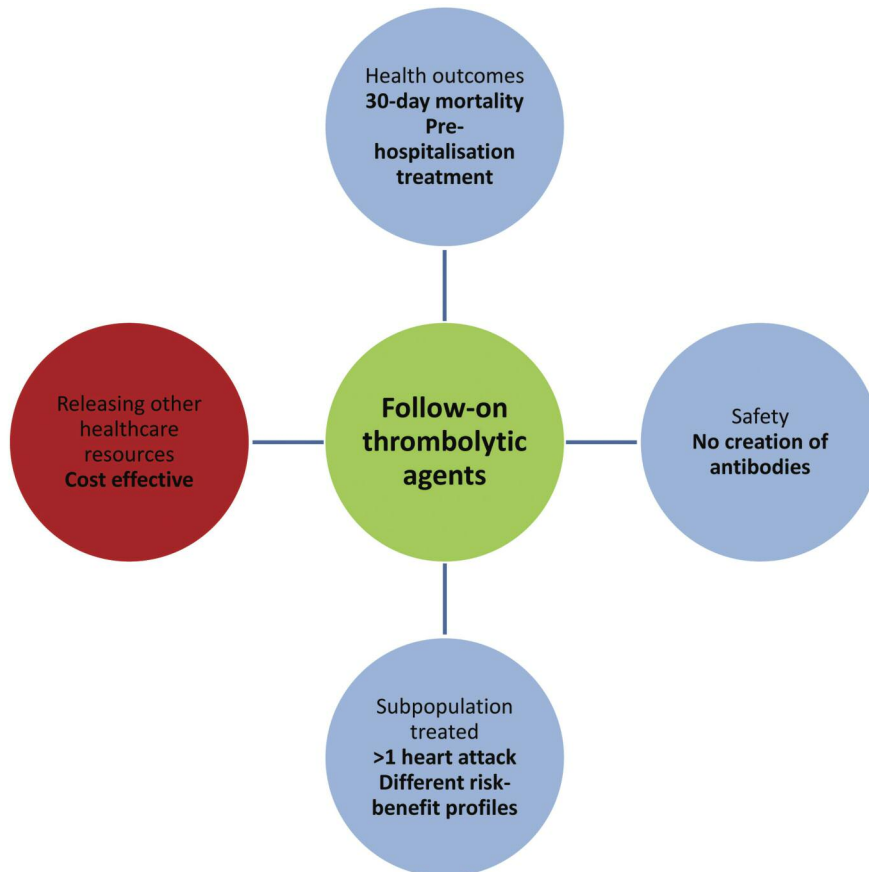
NICE (2002) has recommended all the newer thrombolytic agents for use in patients who have had a heart attack, although benefits and risks for the individual patient have to be taken into account when deciding which particular agent should be used. These newer agents have also been considered to be

more effective in terms of 30-day mortality following AMI, and have an acceptable incremental cost effectiveness ratio (ICER) when compared to streptokinase, the first-in-class medicine.

The latest thrombolytic agents (reteplase or tenecteplase) can be given before the patient reaches hospital. These two agents are new modified forms and can be given by rapid intravenous bolus injection, rather than infusion. This might be very useful in improving health outcomes, especially for communities a long way from a hospital with emergency facilities.

Figure 4.13 summarises the innovatory characteristics of the newer thrombolytics.

**Figure 4.13 Newer thrombolytic agents vs. first-in-class (streptokinase)**



*Source: Adapted from NICE (2002)*

## 5. Value of Having Follow-on Products

There are advantages from having dynamically competitive R&D even though – indeed partly because – this can lead to more than one company launching a new product in a particular therapy area. The potential advantages of dynamic competition are discussed separately in this chapter because they are distinct from the valuable attributes of individual medicines, such as were illustrated and discussed in the previous chapter. The potential advantages of dynamic competition have three aspects:

- Price competition
- R&D spillovers
- R&D competition

We discuss each in turn. To the extent that they occur, they are not a reason to reward any medicine with a higher price. They are, however, reasons why third party-payers should not be automatically averse to the advent of more than one product within a single therapeutic area.

### *Price competition*

The existence of various substitutable treatments within a therapeutic area creates the possibility of competition between medicines well before loss of exclusivity enables competition from generic medicines. Whether competition between medicines is realised depends on the incentives for prescribers: where they have no reason to take into account the comparative costs of treatments as well as their effectiveness competition is likely to be ineffective. But incentives such as physician budgets, combined with information on medicines' prices and comparative performance, can make competition between molecules a reality. The possibility of price competition as a result of the introduction of follow-on products is somewhat restricted by price regulation in many pharmaceutical markets.

We are aware of only one published post-2000 analysis of competition between medicines in a therapeutic class (Lexchin, 2006 – see below) but a number of earlier studies show evidence of active competition. For the US, where market forces play a more significant role than in Europe and price regulation is less pervasive, Di Masi (2000) showed that the majority of new drugs are launched at discounts to both the class price leader and to the average price in that class. This author analyses 1995-1999 US data for a number of conditions. The US Congressional Budget Office's report on drug competition in the US also shows that when one or more follow-on products enter the market, the rate of growth of list prices for market leaders is slowed down. This report also shows that these follow-on products usually enter at a price discount versus the price leader (Congressional Budget Office, 1998). Lu and Comanor (1998), using older US data for the period 1978-1987, show a similar result: increasing the number of competing branded products has a negative effect on launch prices.

Lexchin (2006) analyses the Canadian market (33 drugs in 16 therapeutic classes launched between 1994 and 2003), where prices are regulated. He shows that the mean introductory price of the 33 new medicines was 96 per cent of the price of existing brand-name products and 92 per cent of the price of the most expensive brand-name products in their class. Most of the drugs were priced near or equal to the mean price of the existing branded products and two of them came in with discounts of more than 30 per cent. He also finds that the number of competitors was important in driving price competition. When there were four or more competitors in the class, the prices of new drugs were significantly lower when compared to the classes with just one, two or three competitors.

In Europe, Towse and Leighton (1999) show a similar result for the UK for the period 1969-1998: follower compounds in the mid-1990s typically enter at a price discount to the market leader. An IGES study (IGES, 2002) finds similar results for Germany for the period 1980-2000 for nine therapeutic conditions. Follow-on products in Germany enter the market with a lower price than the original product and gain market share. Moreover, the entry of follow-on products dampens price increases of the original medicine. There is freedom of price at launch in the UK and Germany, a feature which is



not common in most European markets. Reekie's (1998) study of price behaviour in sub-markets across six countries with some form of pricing freedom (Denmark, Holland, Germany, South Africa, the UK and the US) shows that rival products serve a useful purpose in containing market prices.

The story is somewhat different when price competition is analysed in countries with stricter price regulation. For example, Ekelund and Persson (2003) show that in Sweden, the presence of branded substitutes, ie follow-on products, has no effect on launch prices or price dynamics. This result is in contrast to the above-mentioned studies.

On balance, it seems that having more than one drug to treat any condition can generate price competition if prescribers are appropriately incentivised and the price regulations enforced are flexible enough to allow for this – albeit that we are not aware of any more up recent studies than those referred to in this section. Price competition generates savings to payers even when drugs are on-patent.

### ***R&D spillovers***

Henderson and Cockburn (1996) show there are spillover effects in pharmaceutical R&D. Firms have an advantage through economies of scope rather than economies of scale, ie it is less costly to undertake any two R&D projects within the same company than in two different companies. This implies that spillover effects exist between R&D programmes within the company. Thus, additional R&D by any firm, even if it leads only to follow-on products coming into a market, can result in positive externalities for R&D in other disease areas.

Cockburn and Henderson (1994) have also shown the importance of externalities between mainstream pharmaceutical companies, ie spillover effects that occur outside companies. The evidence presented by these authors shows a strong correlation between a company's own innovative achievements and the success of rival firms' efforts. These spillovers come via routes such as the scientific literature and scientific meetings, because successful companies have to publish as well as patent, which brings benefits to the research efforts of others working in the field (Kettler and Towse, 2002). R&D has, through this second externality, positive spillovers to other competing R&D based companies. In other words, organisations that invest in R&D benefit from the R&D of other organisations in the industry.

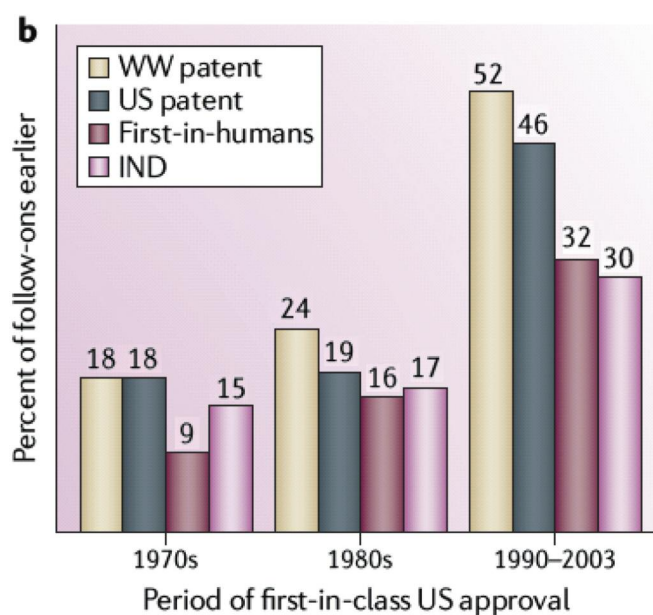
A third element of R&D spillovers occurs via the interactions between publicly-funded medical research and private sector R&D. The literature highlights a number of mechanisms facilitating the transmission of knowledge between the public and the private sectors, including universities (taken to represent publicly-funded research), networking and social interactions and 'absorptive capacity' (for a summary of the literature, see HERG et al., 2008 and OHE, 2009). The third transmission mechanism, 'absorptive capacity', relates to the possibility for firms to assimilate and exploit existing information to create new knowledge – and thereby to appropriate some of the returns accruing to investments in new knowledge made by others (Cohen and Levinthal, 1989). The conventional wisdom, as argued by these authors, was that R&D generated only one product – new information. However, the possibility for firms to assimilate and exploit existing information – the firm's 'learning' or 'absorptive' capacity – represent an important element of a firm's ability to create new knowledge.

### ***R&D competition***

As well as positive externalities or spillovers derived from R&D, as discussed above, there is also competition in pharmaceutical R&D. As Scherer (2010) argues, R&D investment decisions are driven by demand-pull or science-based incentives. These incentives create the potential for profit that companies compete to exploit. Thus, different companies might be simultaneously investing resources in R&D for the same therapeutic area without knowing whether they will be first to the market.

There are contrasting views on whether having follow-on drugs in a therapeutic area is on balance useful (for instance, because they yield price competition and spillover benefits) (see Angell, 2004; and Hollis, 2005). Implicitly the argument that R&D on follow-on drugs is wasteful is underpinned by the notion that research on follow-on drugs only takes place once the first-in-class medicine has been successful. But this is often not the case. DiMasi and Paquette (2004) present evidence showing that development of follow-on drugs often occurs contemporaneously with that of the first-in-class medicine. DiMasi and Faden (2011) reinforce this view with evidence from new data, building on the DiMasi and Paquette (2004) work. In this new work, the authors include first-in-class compounds approved up to 2003 and follow-on drugs approved up to 2007 (ie more recent evidence compared to DiMasi and Paquette (2004)) as well as patent data.

**Figure 5.1 Imitation or development race?**



*Source: DiMasi and Faden (2011)*

Figure 5.1, from DiMasi and Faden (2011), shows the percentage of follow-on drugs approved in the US from 1970 to 2007 that had a first patent filed anywhere in the world (WW patent), had a first patent filed in the US (US patent), were first tested in humans anywhere in the world (first-in-humans) or had an investigational new drug filed (IND), before the first-in-class drug. For instance, for the period 1990-2003, for those follow-on drugs approved in the US, 52 per cent had a patent in the US, 46 per cent had been tested in humans, and 30 per cent had an IND filed, before the first-in-class. Hence, it is hard to distinguish meaningfully between R&D that is directed to the first available treatment for any particular indication and to follow-on products. Thus the development of new drugs in a given class is better characterised as a race. However, as noted in Hollis (2004), DiMasi and Paquette (2004) find that approximately one-third of follow-on drugs received a priority rating from the US FDA, suggesting that the other two-thirds were related to follow-on drugs that were deemed by the FDA to be unlikely to confer a significant benefit.

DiMasi and Paquette (2004) show that periods of marketing exclusivity have been shrinking for first-in-class medicines as a result of therapeutic competition. During the 1960s, the mean marketing exclusivity period for the first-in-class medicine was 7.2 years, decreasing to just over five years in the second half of the 1980s, and decreasing even further to under three years for the early 1990s. For the

period 1995-1998 a follow-on product entered, on average, in less than two years (1.7). DiMasi and Faden (2011) have found that the time from first to second follow-on drug between 2000 and 2003 reduced even further, to 1.1 years on average. Moreover, competition from third entrants is also occurring ever-more rapidly. Figure 5.2 summarises these results.

**Figure 5.2 Speed of entry of follow-on drugs**

Period of US marketing approval for first entrant in class	Time from first to second follow-on drug (years)			Time from second to third follow-on drug (years)		
	Mean	Median	N	Mean	Median	N
1960s	13.5	16.1	9	8.3	5.1	5
1970s	5.7	4.2	12	5.2	3.7	8
1980s	3.8	3.5	18	2.8	2.0	15
1990s	2.7	2.0	28	2.2	1.3	14
2000–2003	1.1	1.1	4	NA	NA	NA

NA, not available. Analysis of variance results for testing whether there are differences in means across the time periods for the time to a second follow-on entrant ( $F_{6,64} = 10.20, P < 0.0001$ ) and for the time to a third follow-on entrant ( $F_{5,36} = 2.72, P = 0.0349$ ) showed highly statistically significant differences. Similarly, the Kruskal–Wallis test results are highly significant for both the time to a second follow-on entrant ( $\chi^2(6) = 27.20, P < 0.0001$ ) and the time to a third follow-on entrant ( $\chi^2(5) = 14.94, P = 0.0106$ ).

*Source: Di Masi and Faden (2011) (Table 2)*

The US Congressional Budget Office (Congressional Budget Office, 1998) finds a wider range on pure market exclusivity periods before a similar patented product is introduced (one to six years). Towse and Leighton (1999) confirm similar results for the UK, by showing that the potential for first entrants to establish dominant market positions in the UK has been eroded by faster entry of second and third follow-on products with the same mode of action. The introduction of follow-on products thus brings about competition in the pharmaceutical market. This is consistent with Scherer’s (2010) observation that after taking into account the investment character of R&D expenditure, pharmaceutical companies enjoy returns on investment only two to three percentage points higher than their real cost of capital, which can be attributed to the riskiness of R&D investments. The drawback is that if competition finally dissipates all attainable rents, then investment in R&D becomes less attractive for the industry.

The nature of the market for medicines implies that the pharmaceutical R&D process is not a winner-takes-all race and, as already discussed, the first-in-class medicine should not be assumed to be the best-in-class. Given the high risks and uncertainties associated with pharmaceutical R&D, any compound could fall at the next R&D ‘hurdle’. Thus, multiple compounds for any one therapeutic area are needed to ensure that at least one of them is successful.

## 6. Conclusions

There are five concluding points to make. First, innovation in pharmaceuticals, or indeed any other area, should not be thought of as being either a 'breakthrough' or just a 'me-too'. Innovation is not simply there or not; rather it is a matter of degree and can be present in any one or more of numerous different dimensions.

Second, the ultimate arbiters of the innovativeness of a new product (in the absence of externalities) are the users. For medicines, the 'users' include patients who take the medicines, payers who bear the financial costs, prescribers who decide which medicine is used, and carers who offer support to patients. As highlighted with the case studies above, patients and payers derive value from medicines in numerous ways. Thus, innovation in medicines should be treated as a multidimensional concept: a new medicine may be more or less innovative along any one or more of the dimensions.

Broadly speaking, innovation in medicines can bring about advances in health gains, cost savings in health services, advances in patients' and/or carers' convenience, and/or can generate other societal gains. Any one new medicine may not lead to an improvement in any or all of the characteristics illustrated in this report, but what is important to recognise is that improvements achieved in any of the dimensions can be socially valuable. Payers acting on behalf of patients need to take a balanced approach to ensure they pay an appropriate reward for the socially-valuable innovations. Given the resource costs and time entailed in measuring any aspects of innovation – whether health gains, or time savings to patients' carers, or cost savings to the healthcare system, or improved patient experience of care – it may not be practical or desirable to measure all types of benefit or cost impact on all occasions, but if payers choose to exclude elements of value in their pricing and reimbursement of medicines they should at least justify the exclusions explicitly.

Third, pharmaceutical R&D is a risky process with uncertain outcomes. Consequently (dis-)incentives for innovation can be expected to affect all magnitudes and dimensions of innovation inextricably.

Fourth, the full assessment of innovation of medicines is only possible well after launch; many valuable therapeutic benefits are not appreciated until long after launch. This means that if these drugs are not launched or not used many of these additional benefits will not be realised.

Fifth, the published literature available shows that dynamic R&D competition between organisations drives greater R&D efficiency and productivity as well as the potential for price competition when the result is that more than one molecule is launched within a therapeutic area. For companies, dynamic competition drives their R&D process and decision-making. For payers, price competition can generate savings. Overall, dynamic efficiency reduces the time patients must wait to get access to new technologies and yields differentiated medicines, enabling better matching to different patients' needs.

The existence of a range of medicines is increasingly important in an era of stratified medicine, where the objective is to manage groups of patients with shared biological characteristics by using molecular diagnostic testing to select the best therapy in order to achieve the best possible medicinal outcome for that group. We are already observing some cases of stratified medicine, especially in cancer. While having a range of follow-on drugs might appear ex post to be inefficient, ex ante competition stimulates the creation of medicines suitable for different sub-groups of patients. Such stratification can help create new, better, focused applications for existing medicines in given therapeutic areas, generating new differentiation post-launch. In the long run, ensuring the conditions are in place to generate appropriate dynamic competition between medicines will be important. R&D competition is an important feature of all R&D-based industries, not just in the life sciences sector.

The overall consequence of these five major points is that any policy that does not recognise all aspects of value as well as the costs to the payers, and that has the potential to increase the uncertainty of future earnings if a company fails to launch the first-in-class medicine, might end up discouraging potential worthwhile R&D investment, rather than encouraging it. Pricing and reimbursement, or Health Technology Assessment (HTA) regulation, that ignores or subverts the five previous concluding points risks stifling socially-valuable innovation.

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