THE MANY FACES OF INNOVATION

by OHE Consulting for

The European Federation of Pharmaceutical Industries and Associations (EFPIA)

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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 either "breakthroughs" or "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 consumer 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 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 payers in Europe to recognise and reward innovation beyond a very limited definition of the term. In many European countries cost containment policies are being implemented in the pharmaceutical market based on some definition of "innovation" in medicines.

A prominent recent example is the new German reference pricing system. Medicines that are considered to be 'non-innovative', using a particular and narrow view of innovation, will be included in the reference price system, irrespective of their patent status. Only those patented products having a therapeutic improvement will be excluded from this mechanism. The definition of added therapeutic value currently being applied by the Gemeinsamer Bundesausschuß is, however, a narrow one. A recent reform announced by the Spanish Ministry of Health includes an evaluation of the therapeutic utility/interest of new medicines. Only those products with an "exceptional" innovation level will be reimbursed without delay and with a price premium. It is still unclear how "exceptional innovation" will be defined, but it is likely that the definition will also be a narrow one. If these types of policies continue, many new medicines with valuable, improved characteristics may be treated as if they are no different from generic copies of existing products. This is likely to act as a disincentive to pharmaceutical research and development (R&D) in general.

Another policy which is gaining momentum among European regulators is selective financing of medicines. Under such a policy, obtaining reimbursement status, i.e. being included in the positive list or formulary, will depend on the medicine's degree of 'innovativeness'. An important factor that will determine the ultimate impact of the new mechanisms on the pharmaceutical industry as a whole is, therefore, 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 understand 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.

The relationship between reimbursement mechanisms and rewards for innovation has been recently 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 are the reason why companies are deciding to launch their products in the US (rather than Europe).

The purpose 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 therapeutic value.

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

2. Characterising innovation in general

Innovation happens in all areas of economic activity. Where there are 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. This is because the consumer is both the end user and the payer.

In the case of prescription medicines the consumer/patient is often not the main decision maker about whether to consume – the prescriber takes a major role – and is also often not the payer for the medicine consumed, or only pays a part of the price. The payer is usually a third party, via tax-funded health services or social or private insurance. As a result it is more difficult to use market forces to determine the innovativeness of new medicines. But the principle that an innovation is something that the ultimate consumer, the patient, finds more useful than what has gone before, remains.

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 the basic science, economics, corporate management and marketing, as it proceeds through "the exploration and exploitation of opportunities for a new or improved product, process or service" (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 adopted by other parties beyond the discoverers. Innovation implies not only a technological advance but also one that brings social and economic consequences. In many cases the full value of an innovation is not recognised when the invention is made or the innovation is introduced. It can take time until an innovation is appreciated by the market.

Thus innovation can be on a large or small scale, and can have any of a very broad range of socially-relevant characteristics. Innovation is not 'on or off', 'black or white'; it is a matter of degree. Neither is innovation limited to a narrow range of aspects; it can include anything that people find useful. Innovation is not a process of duplication but rather a process of evolution. Thus, it is inadequate to characterise innovation based on static criteria.

Innovation can occur as a result of both public and private R&D. Our focus in this paper is on private R&D.

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 i.e. its (discounted) expected net future earnings outweigh its (discounted) R&D 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; and
- 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 might respond to existing patterns of demand but it can also create a new demand 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 a product innovation allows a firm to gain a temporary competitive advantage, which can originate from a patent or the length of the imitation process of 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). Rosenberg (2001) goes beyond this simplified model of innovation, which overlooks the role of uncertainty associated with new technologies and assumes that an innovator firm has only to introduce a new technology into the market and automatically gains its rent. The innovation process involves a fundamental element of uncertainty, especially with respect to the ultimate characteristics and hence 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 and educational systems, affects the innovation

process by setting the rules and range of opportunities for innovation (OECD, 1997). 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 (e.g. wage schemes, tax allowances, intellectual property rights, government subsidies for R&D) and non-pecuniary (e.g. prestige, status); and
- 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, each body of knowledge can determine the opportunities of technology progress and suggest possibilities for designing new products, or improving the performance of existing ones, or 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 plays a major role in the process of innovation.

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 be hardly anticipated ex ante. Innovators aim to successfully 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; and

- 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). 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.

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 derive a significant economic impact through the processes of "learning by doing" and "learning by using". These can be defined as follows:

- "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 lead 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).

2.3 Innovation is a cumulative activity – small steps are important too

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, though 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, physicians, academics, governments, international organisations) and its influence is not restricted to the pharmaceutical sector but is crucial for the entire economy.

Innovation can take many dimensions, and for this reason, it is misleading to attempt to measure the degree of innovativeness of any one medicine with a single indicator. Until now, new medicines are commonly referred to as being either a 'breakthrough' or a 'me-too'. If we use this classification for a moment, a breakthrough or major innovation could be 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 could then be 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 arises from using this binary classification is the pejorative sense the term 'incremental' takes. Innovation in pharmaceuticals should not be classified using this dichotomy, given its complexity and multi-dimensionality. 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.

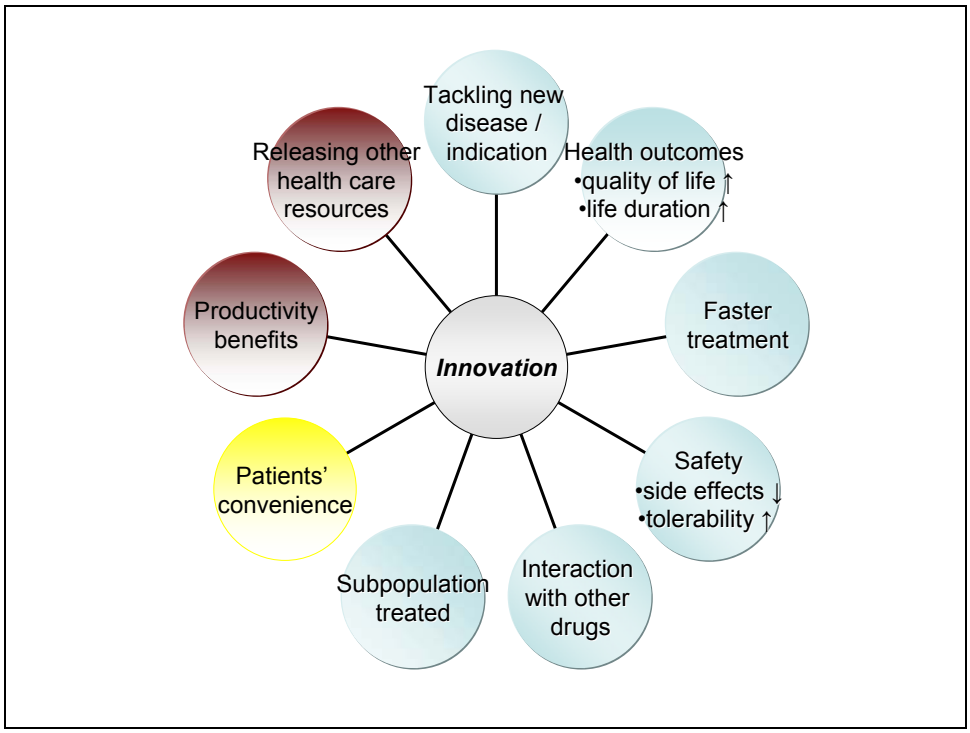
We have already argued that an invention becomes an innovation when it is successfully implemented and adapted in the market place. This implies consumers, as final users and payers, have to both value the invention and be willing to pay for it. For pharmaceuticals, however, there is a need to make a distinction between the final user (i.e. 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, or both.

Figure 1 summarises the numerous different characteristics, or attributes, of innovation that need to be taken into account in any discussion of innovation in the pharmaceutical industry. These attributes can be grouped under three more general headings:

- Health gains;
- Patients' convenience (which will often be linked to better health outcomes); and
- Other societal gains.

Examples in practice of all the possible elements of innovation shown in Figure 1 are presented and discussed in section 4.

Figure 1 Characteristics of Innovation in Pharmaceuticals



Under the heading 'health gains' (shaded blue in Figure 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;

3. Faster health improvement (E.g. 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 – QALYs, etc.);

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 (i.e. first-in-class) or by offering some form of health gain versus existing treatments. Not all medicines are life-saving but may offer relief and/or improvements in quality of life.

'Patients' convenience' (shaded yellow in Figure 1) includes any attributes which improve patient convenience and hence both satisfaction *per se* (for instance, by reducing patient discomfort) and also greater adherence to treatment, which leads to better health outcomes. Examples of such attributes can include new presentations or delivery methods of existing molecules, such as patches; 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.

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 health care resources' and 'productivity benefits' (shaded red in Figure 1) are benefits that accrue mostly to the providers of health care services, or to the economy as a whole, rather than to the individual patient. 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 health care is provided to a group of patients then other resources (including non-health care 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 altogether the need for hospitalisation. New medicines can also lead to productivity gains as a result of patients or carers returning faster to work or not missing work at all, or to them being more productive when they are at work.

Section 4 of this paper (below) illustrates with examples how individual medicines or classes of medicines bring about improvements in the dimensions shown in Figure 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 emphasizing.

Figure 1 characterises innovation as a multi-dimensional phenomenon at any one point in time, i.e. 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 a high degree of serendipity and creativity which cannot be planned. 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. They show that for the top 20 best selling drugs in the US in 1993, by 1995 40% 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% of sales. However, Pritchard et al. find a skewed distribution, with a significant number of products having no subsequent indications and 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: some specific examples

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

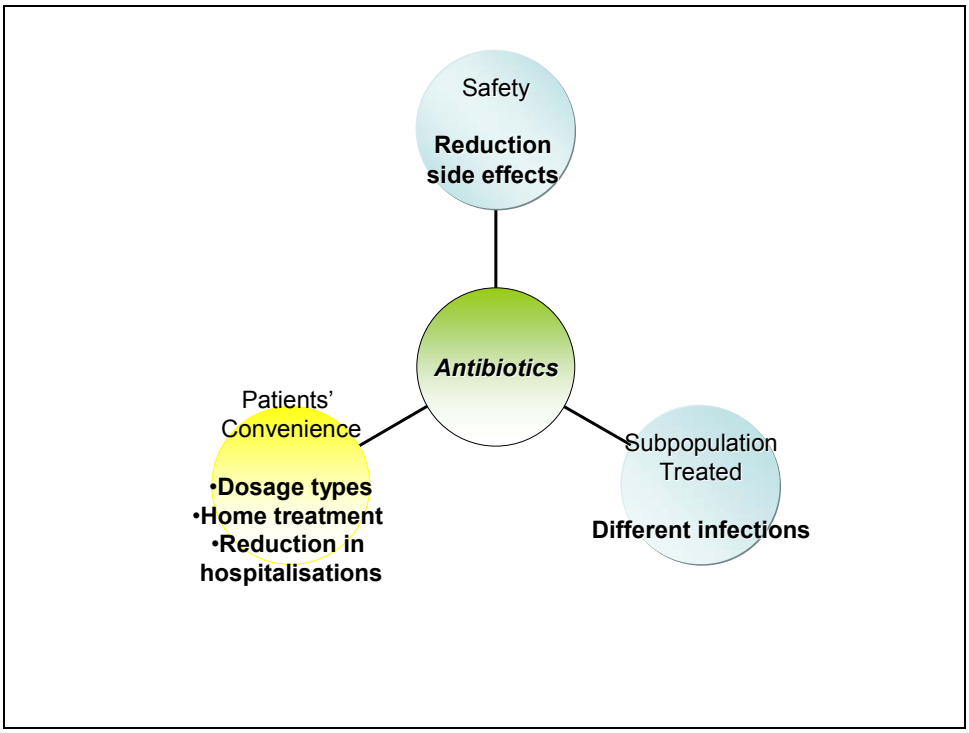
4.1 Examples of older medicines

Antibiotics

The antibiotic penicillin G was firstly obtained in 1940. This substance had several limitations in its use, so, as a result, several modifications of antibiotics were developed, with the result that antibiotics could be used in a wider context.

In addition, new antibiotics, including cephalosporins, were developed to respond to the emergence of antibiotic-resistant bacterial strains. When first introduced in the 1960s, the first cephalosporin 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 infections (and hence different subpopulations). In addition, they are available in different dosage types, 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 health care costs. Figure 2 shows these improvements schematically, highlighting the elements of Figure 1 that are most relevant to this example.

Figure 2 Evolution of antibiotics



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 duration of action. This implies that the use of such medicines can lead to more personalised treatments. In addition, the possibility of delivering corticosteroids by inhalation has the potential to improve patients' convenience.

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.

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 last 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 at al., 2001). The reduction in sedation effects have reduced work-related accidents and lost productivity.

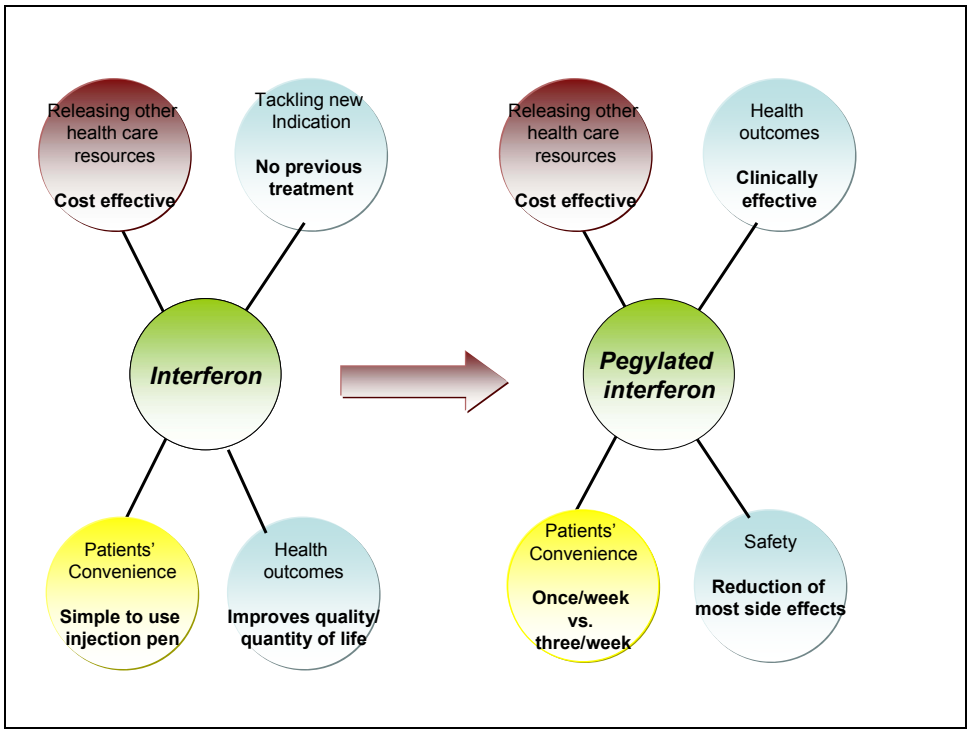
4.2 More recent examples

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% of the 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. Drop out rates have been estimated to be around 7-14%.

Recently a new type of interferon alpha has been introduced, the pegylated interferon. In the last years, two product licenses have been granted for this new type of interferon alpha for the treatment of Hepatitis C. Figure 3 shows the evolution of available treatments for Hepatitis C, highlighting dimensions of innovation which have been improved as a result of these new medicines. The dimensions refer back to Figure 1.

Figure 3 Evolution of available treatments for Hepatitis C



Source: Adapted from NICE (2004), ABPI (1998)

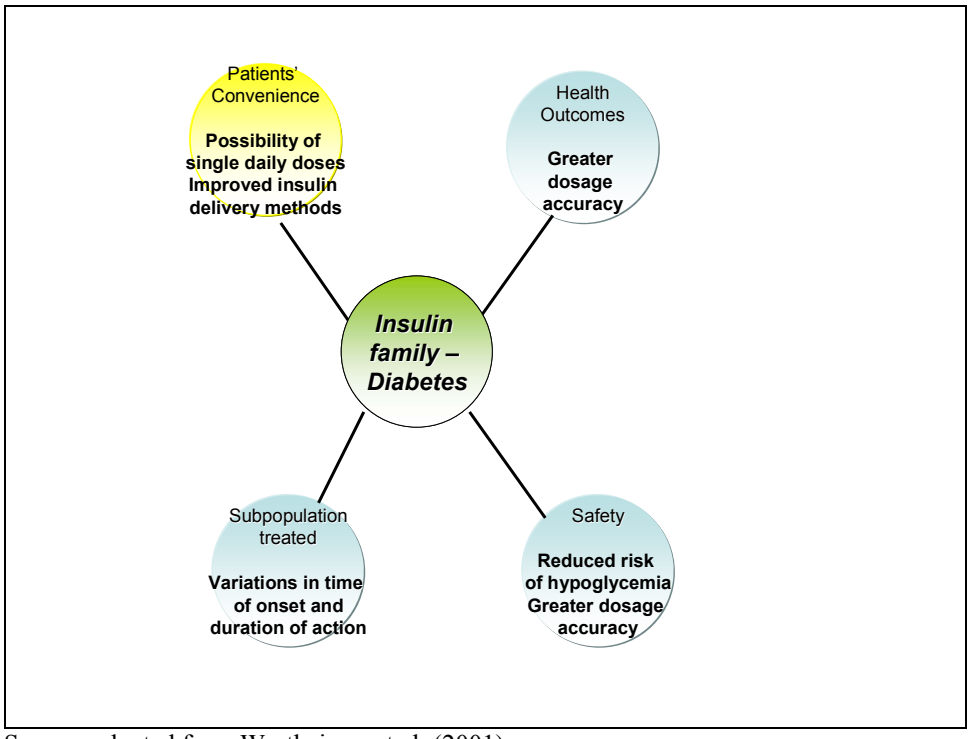
Evidence provided by the UK's National Institute for Clinical Excellence (NICE) shows that the pegylated interferon is both clinically and cost effective compared with interferon alpha (NICE, 2004). Hence, while interferon alpha provided the first treatment for Hepatitis C, the pegylated interferon has provided additional benefits as a result of improved health gains, including reducing most side effects, improved patients' convenience and cost savings. Figure 3 illustrates this schematically: highlighting just those dimensions of innovation

(shown in Figure 1 earlier) where pegylated interferon is most clearly differentiated from interferon alpha.

Diabetes

The insulin molecule has been extensively manipulated to provide a range of insulin products used 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 being done 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 4A shows how the wide range of insulin products affects positively some of the different dimensions of innovation from Figure 1.

Figure 4A Insulin treatments for diabetes



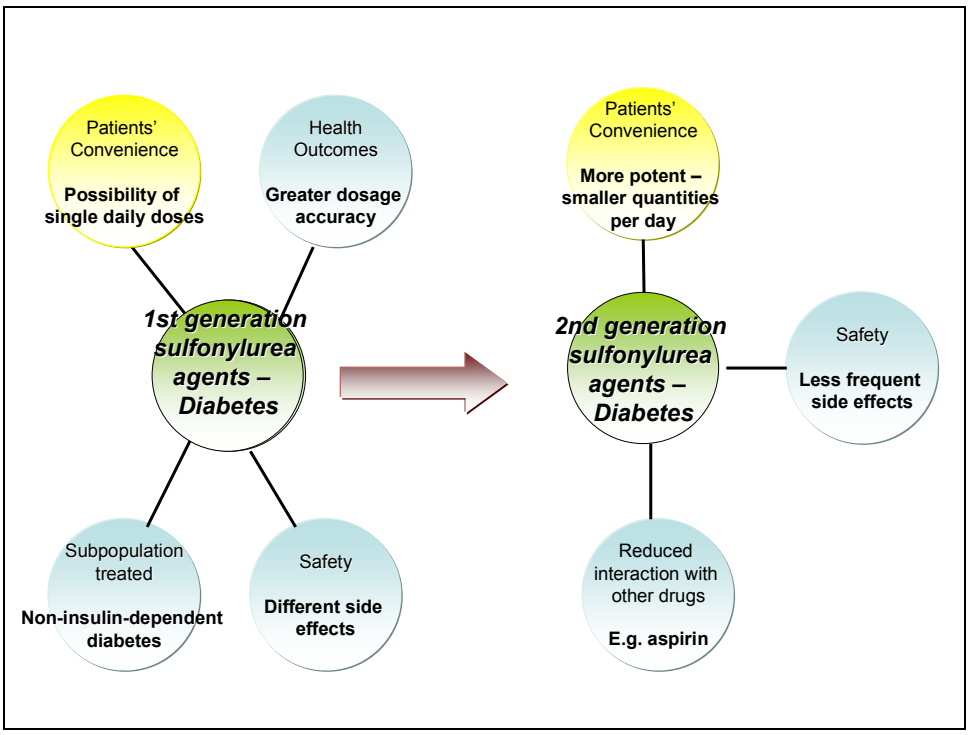
Source: adapted from Wertheimer et al. (2001)

Treatments for non-insulin-dependent diabetes are also available: oral glucose-lowering drugs. By the end of the last decade, 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 that were 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 agents available. Although of similar molecular structure to one another, 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 4B.

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 4B.

Figure 4B Non-insulin treatments for diabetes



Source: adapted from Wertheimer et al. (2001)

In early 2000, a new type of 'oral glucose-lowering drug' was introduced, the glitazones. This new class of drugs is especially indicated for those patients who suffer unwanted or harmful side effects from the use of metformin or a sulfonylurea (NICE, 2003a). This new form is thus able to treat a subpopulation with lower side effects.

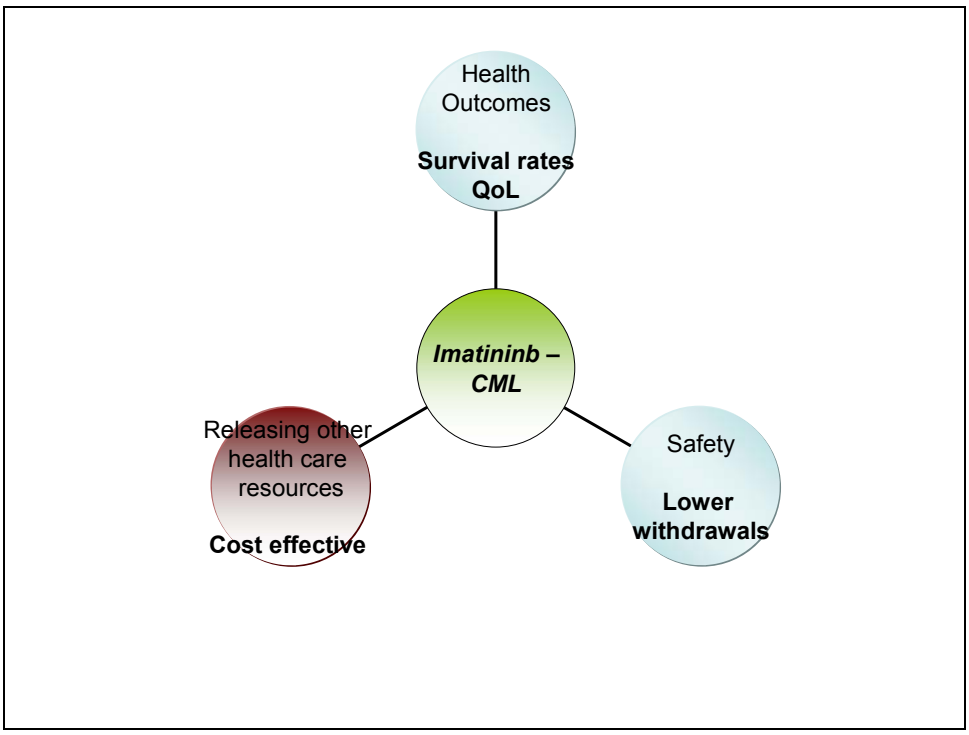
Chronic myeloid leukaemia

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 these produce intolerable side effects for around a quarter of people with CML (NICE, 2003b), including flu-like symptoms.

The introduction of imatinib 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 current 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 lower with imatinib. Figure 5 shows the improved attributes as a result of imatinib. In spite of the important improvements offered by this new product, interferon alfa for the treatment of CML remains useful in some patients (ABPI, 2004).

Figure 5 Imatinib – improvements for the treatment of CML



Source: adapted from NICE (2003b)

Rheumatoid arthritis

The current treatments for rheumatoid arthritis (RA) consist of a sequence of disease-modifying antirheumatic drugs (DMARDs), which should be administrated soon after diagnosis. In particular, the current best practice is for initial treatment with methotrexate (NICE, 2002a; Blumenauer et al., 2003). As the "medical review panel" of the Arthritis Foundation emphasized, "six years ago, if you had RA that didn't respond to DMARDs, you were out of luck" (AF, 2004). Today, the subgroup of patients who fail or are unable to tolerate traditional DMARDS can be treated with etanercept and infliximab, which are

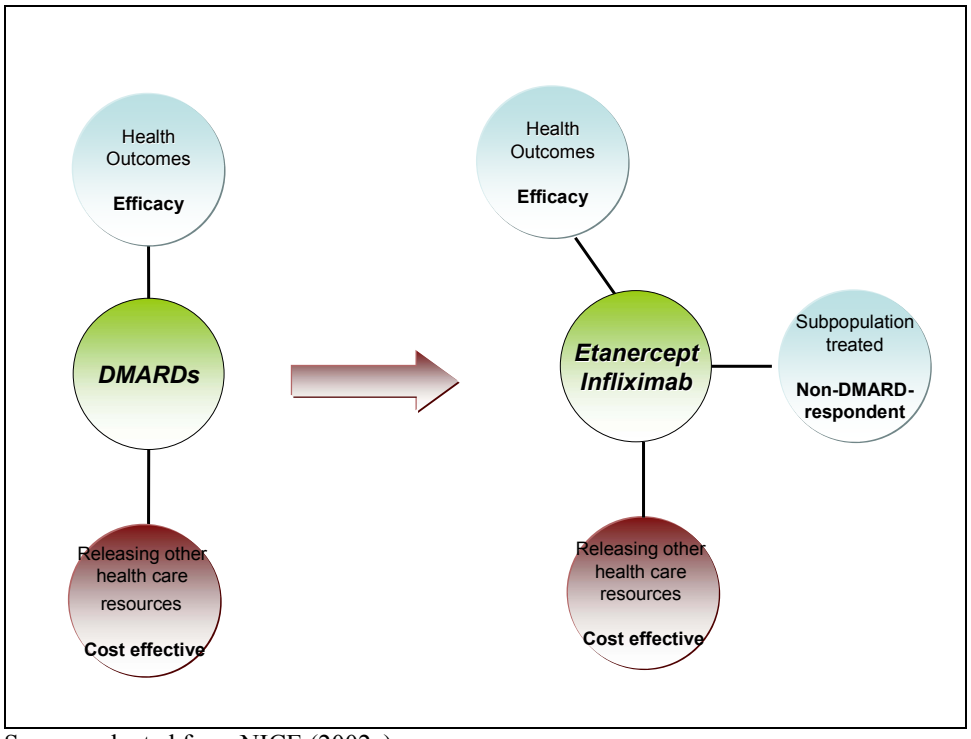
biological agents that inhibit the action of tumour necrosis factor (TNF), thus suppressing inflammation.

Clinical evidence for etanercept show a statistically significant difference in ACR20 responses (20% improvement in American College of Radiology symptom score) at three and six months (NICE, 2002a). Results of a Cochrane review indicates that 12 month radiographic data showed overall improvement versus methotrexate (Blumenauer et al., 2003).

Results of clinical trials comparing infliximab in combination with methotrexate versus methotrexate alone show a statistically significant difference in ACR20 responses at 30 weeks (50% vs. 20%) that were maintained at 54 and 102 weeks. In addition, NICE has estimated the incremental cost effectiveness ratio of both therapies to be in the acceptable region.

Figure 6 shows the improvements delivered by both infliximab and etanercept vs. DMARDs for the treatment of RA.

Figure 6 Anti-TNFs vs. DMARDs: additional benefits for the treatment of rheumatoid arthritis



Source: adapted from NICE (2002a)

The methods of administration of infliximab and etanercept are different. The former is given by intravenous infusion with co-administration of methotrexane weekly, and the latter is given by subcutaneous injection twice a week. As NICE noted, a wide use of infliximab can lead to a "greater demand of day-case facilities", while a widespread of etanercept can result in a "greater demand of outpatient facilities".

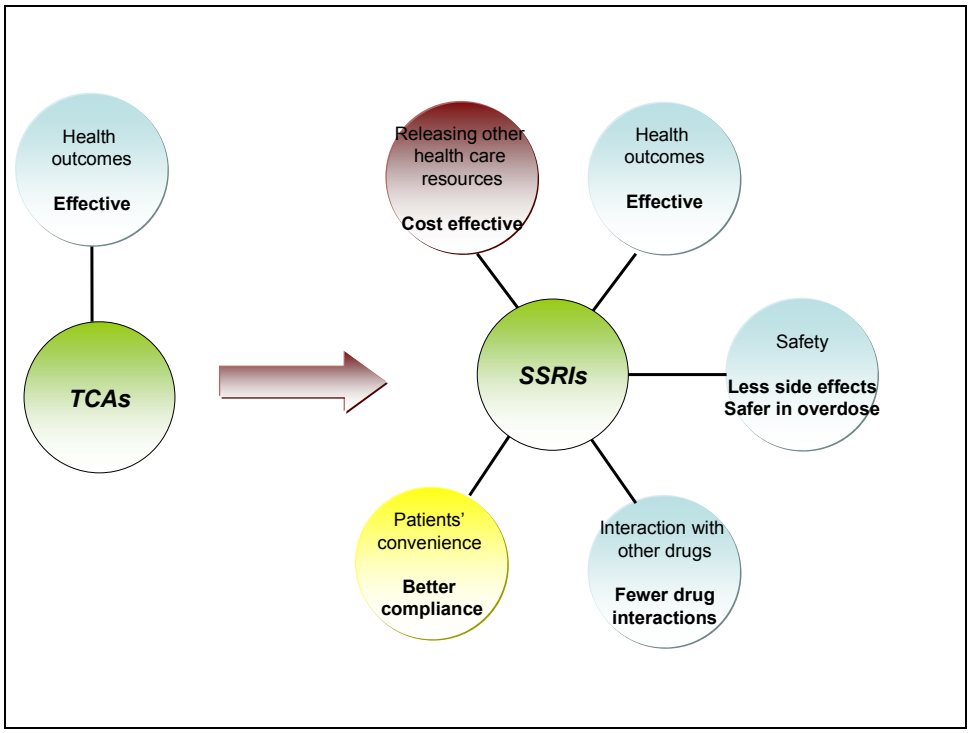
Depression

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). These were developed in the late 1980's 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 challenge the view that SSRIs are expensive. Combining clinical outcomes with a full range of health care costs suggest that the high price products may be more cost effective. In particular, Stokes et al. (1997) highlight that fluoxetine can reduce health care 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 7 illustrates these improvements.

Figure 7 Evolution of antidepressants: from TCAs to SSRIs



Pharmacological considerations suggest that SSRIs are a heterogeneous class (Cipriani et al., 2003). There are differences in both their primary pharmacological action (i.e. selective and potential inhibition of serotonin reuptake) and their secondary action (e.g. blockade of norepinephrine and domapine 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 major depressed patients in terms of response to SSRI treatment: about 30-40% 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% of non-responders to fluoxetine did respond to sertraline (Zarate et al., 1996). Another study has shown that 63% 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% (Joffe et al., 1996). Regarding differences in economic evaluation among individual SSRIs, a recent review by Croom et al. (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 discounts relative to both the class price leader and to the average price in the class.

Thrombolytics

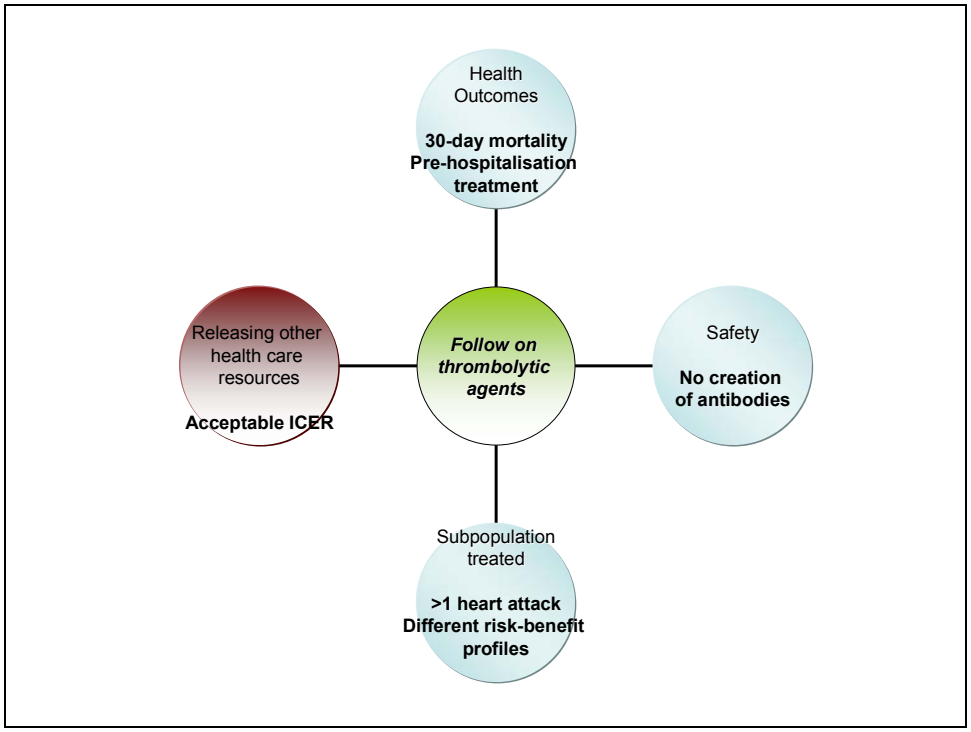
The first thrombolytic agent to treat acute myocardial infarction (AMI) was streptokinase. This agent was an important evolution in the treatment of AMI. However, streptokinase can only be used once because people using this agent develop antibodies in their blood preventing streptokinase from working 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 (2002b) 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, 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 8 illustrates the innovatory characteristics of the newer thrombolytics.

Figure 8 Newer thrombolytic agents vs. first-in-class (streptokinase)



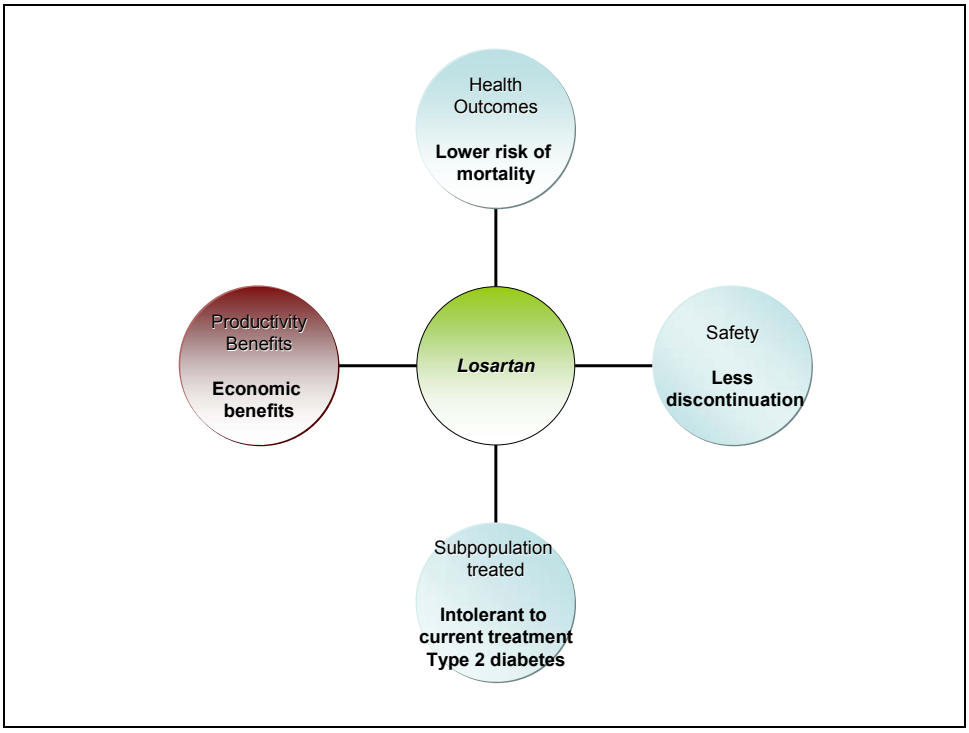
Source: adapted from NICE (2002b)

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 to significantly 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 9 shows these improvements schematically.

Figure 9 Improvements relative to ACE inhibitors derived from the first AIIA



Follow-on AIIAs have been introduced in the market, which can lead to additional benefits versus the first AIIA. 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., 2001). 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 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.

5. Value of having follow-on products

There are also additional advantages of having follow-on products in any one therapeutic area. These are not characteristics of innovation, as illustrated in Figure 1, but are factors that need to be considered in any discussion about the innovation process in the pharmaceutical industry.

These non-innovation advantages have three aspects:

- Price competition;
- R&D spillovers; and
- R&D competition.

We discuss them in turn.

Price competition

There is evidence that shows the existence of price competition in different therapeutic areas as a result of having various substitutable treatments available. However, the possibility of price competition as a result of the introduction of follow-on products is somewhat restricted by the degree of price freedom. For the US, where market forces play a more significant role than in Europe, Di Masi (2000) shows 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 in 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 (CBO, 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.

In Europe, Towse and Leighton (1998) 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, 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 a country with stricter price regulation (Sweden) the presence of branded substitutes, i.e. follow-on products,

has no effect on launch prices or price dynamics. This result is in contrast to the above mentioned studies.

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, i.e. it is less costly to undertake any two R&D projects within the same company than in two different companies. This implies 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, i.e. spillover effects that occur *outside* companies. The evidence presented by these authors demonstrates that output shows a strong positive correlation between own output 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 leading to follow-on products has, through this second externality, positive spillovers to other competing companies.

R&D competition

As well as positive externalities, there is also competition in pharmaceutical R&D. Different companies might be investing resources in R&D for the same therapeutic area without knowing whether or nor not they will be the first one to the market. Having fewer (or no) follow-on products as a result of drugs being pulled near launch because someone else was first to the market implies there will be far more 'failures'. Alternatively, there could be fewer parallel R&D programmes across companies as these companies back off at an early stage if they think another company is ahead, which implies we can again lose some of the spillover effects we have just discussed. The nature of the market for medicines implies that the pharmaceutical R&D process is not a winner-takes-all race, and as shown in previous sections, the first-in-class medicine should not be assumed to be the best-in-class.

New evidence shows that development of follow-on drugs often occurs contemporaneously with that of the first-in-class. Thus R&D in the pharmaceutical industry is simultaneous, so it is hard to meaningfully distinguish between R&D that is directed to the first available treatment for any particular indication and to follow-on products (DiMasi and Paquette, 2004).

In addition, DiMasi and Paquette (2004) show 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 (1.8). The Congressional Budget Office (CBO, 1998) offers a wider range on pure market exclusivity periods before a similar patented product is introduced (one to six years). Towse and Leighton (1999) reinforce DiMasi and Paquette's results, 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 follower products with the same mode of action. The introduction of follow-on products thus brings about competition in the pharmaceutical market.

6. Conclusions

Innovation in pharmaceuticals, or indeed any other area, should not be described as binary i.e. a medicine either being a breakthrough or a me-too, it is a matter of degree and can be present in any one or more of numerous different dimensions. The ultimate arbiter of how innovative a new product is, if it is at all, the final user: namely the patient in the case of medicines; and patients derive value from medicines in numerous ways. Thus, innovation in medicines should be treated as a continuous (as opposed to discrete) and 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, advances in patients' convenience, and/or can generate other societal gains. These other societal gains include releasing other health care resources as new medicines enable a change in the way health care is provided to a group of patients and improved productivity.

Any one new medicine may not lead to an improvement in all of the characteristics illustrated in this report, but what is important to recognise is that improvements in any one of the dimensions can be socially valuable.

Given the peculiarities of the pharmaceutical market, it is usually a third party payer who acts as the agent for patients, so it is the payer who should try to evaluate patients' willingness to pay in setting reimbursement. For patients their health will be the most important factor, not price. Payers, however, take a different view, attaching greater importance to limiting expenditure. Payers acting on behalf of patients need to take a balanced approach to ensure they pay an appropriate reward for the socially valuable innovations and avoid the problem of over-consumption as a result of patients receiving medicines for free.

Any policy, including those mechanisms which focus prominently on cost-saving criteria, with the potential of increasing 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.

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