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INNOVATION IN MEDICINES: CAN WE VALUE PROGRESS?

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This is a summary of the main points and conclusions from a discussion Forum prepared and facilitated by the Office of Health Economics for Pfizer Limited, who funded both the event and the production of this Briefing. The views reproduced here are the author's synthesis of the discussions at the Forum (in which he participated) and have been agreed on that basis with the Forum participants. Thus the arguments and views presented in the text, unless stated otherwise, cannot be attributed to any one of the Forum participants individually or to them all collectively.

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The Forum took place on 25th September 2009 at the Science Museum, London. It was chaired by **Dr Keith Smith (Director of Science and Innovation Analysis, Department for Business, Innovation and Skills)** and the other participants were:

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1. Background to the discussion

The pharmaceutical industry has expressed concern that the process of innovation is not adequately taken into account in the practice of health technology assessment. Professor Sir Ian Kennedy noted in his July 2009 report to the Board of the National Institute for Health and Clinical Excellence (NICE) that the Association of the British Pharmaceutical Industry's (ABPI) submission to his investigation argued that "the failure to recognise or reward innovation in one area may compromise an entire pathway of ... follow-on developments" (Kennedy, 2009).

The process of pharmaceutical discovery and development is unpredictable and non-linear and takes many years from initial research to marketable product,

if any. Frequently, one innovation leads to another by yielding new knowledge and opening up new, sometimes unexpected, avenues of research and learning, which can result in further new medicines in future (Pritchard, 2001). The pharmaceutical industry has stated its concern (see above) that a failure to recognise and adequately reward innovation in one area or a failure to take an explicitly long-term perspective may compromise an entire pathway of future, currently unidentified, follow-on developments in medical technology of benefit to patients.

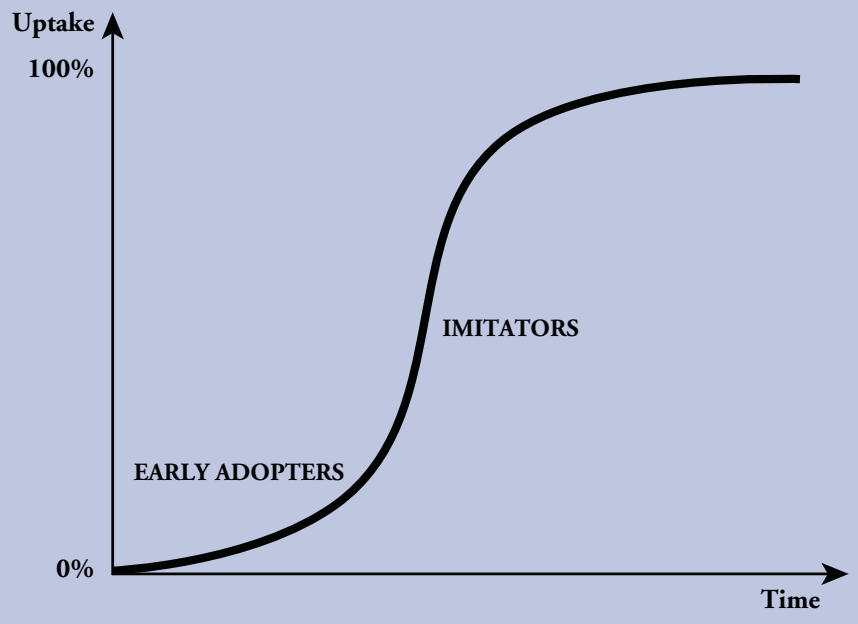
For most goods and services the take-up of innovations usually follows a pattern of initially slow spread among a relatively small minority of users, the 'early adopters', who are eventually imitated by the majority. A stylised representation of the resulting S-curve pattern of cumulative take-up of an innovation over time is illustrated in Figure 1. But diffusion patterns are critically linked to, and constrained by, the nature of the market. For example, complementary assets and capabilities needed to fully realise the benefits of a new technology may initially be lacking and need time to develop (e.g. diagnostics may need to improve or spread before the full benefits of a new medicine can be realised).

Medicines are, around the world, bought and sold within tightly mediated markets and health technology assessment (HTA) is increasingly becoming a major tool of mediation by the State and other payers. This brings with it the possibility that the diffusion of innovations in the pharmaceutical sector could on occasions be choked off if HTA bodies determine against technologies too soon and thereby prevent early adoption or subsequent imitation. The Forum met to discuss how realistic this possibility appeared to be and, should it arise, whether the appropriate policy response would include changes to HTA.

The measurement of value in HTA, as undertaken by the National Institute for Health and Clinical Excellence (NICE) in England and Wales and by other HTA bodies internationally, captures many aspects which matter to patients and to society as a whole, but not all (see the debate summarised by Kennedy, 2009). The problem of appropriately recognising in HTA where future innovation potential is expected to be significant exacerbates other 'market failures' around innovation path dependency. That is, there are other reasons than HTA processes why the prospect of future sales of further innovations downstream of the current product may be insufficient incentive for investment in R&D now:

- myopia in capital markets - companies may have to pay an unduly high cost for, or may simply not be able to access, funds for R&D investments where part of the payback is expected to be in the very long term;
- there may be information asymmetries between companies doing the research, capital markets and payers for medicines. Companies can be assumed to have the best information about the technologies they are developing but even when they fully communicate this to lenders and payers, those audiences may not accord the information full credibility;

Figure 1: **Innovation adoption in a typical market – stylised**



- payer promises on price may not be believed by companies or investors, particularly if payers have in the past opportunistically lowered the prices they are willing to pay once companies have already incurred sunk costs;

- the existence of spillover externalities may mean that companies underinvest in R&D relative to what would be socially desirable. That is, company 1 researches and develops medicine A but by so doing indirectly helps company 2 to develop and sell medicine B (or even to develop and sell a different kind of product altogether).

The purpose of the Forum on 25th September was to discuss:

- the extent, importance and tractability of any problems arising from innovation path dependency in health technologies;

- key elements of the policy and research agendas for tackling such problems to the extent they arise so as to achieve the right amount and type of innovation via appropriate recognition of long-term benefits of innovation and the balancing of risks and rewards.

The discussion ranged widely. The following paragraphs set out the main points raised and identify both where there was broad agreement and where a range of views remain. During the Forum, some issues recurred at different points of the discussion. The following paragraphs are organised into discrete sections according to the main themes covered. The themes are interrelated and overlapping, however.

2 Is pharmaceutical innovation different?

It was agreed that the market for medicines differs substantially from most other markets for goods or services. Consumers' (patients' and prescribers') willingness to pay for medicines is not communicated by them in markets in the same way as their willingness to pay for most other goods or services. The willingness to pay for medicines is, in the UK as in most other countries, an issue of public policy. In England and Wales, NICE has the job of signalling the extent of the National Health Service's demand for the medicines NICE is asked to evaluate. Thus NICE, a public HTA body, is sending signals about what innovations it will or will not sanction the NHS to pay for.

In England and Wales as in several other countries the government has not adopted a procurement approach to pharmaceutical innovation. (By contrast, a procurement approach is commonly used by governments in the area of defence spending – weapon systems – for example.) That is, the government does not generally go as far as to specify prospectively the kinds of new medicines that the NHS particularly wants and would be willing to pay for, and those it is not interested in. Rather it is left to private sector enterprises to come up with new medicines, and when they do a decision is then taken, with the aid of HTA, about whether the NHS will pay for it at the price proposed by the manufacturer.

Early adopters of innovations in 'typical' markets, where the final consumer is also the payer, are those people who are willing to bear initially high costs and are not put off by uncertainties over the usefulness of the product. Early users of mobile phones were not put off by their high purchase price and high user charges, nor by their physical size, weight and general unwieldiness. As the market grew, the value of mobile phones became better and more widely appreciated, the market expanded, the quality of new mobile phones increased and the unit price of old designs fell, the market expanded some more, and the technology continued to develop, sometimes in quite unforeseen ways.

In medicines markets the dynamic aspect of competition is particularly important, i.e. the competition for existing medicines that comes from the development of new and better substitutes, or at least the threat of that. Even in those cases where static competition for a particular treatment 'market' – i.e. competition from existing alternatives – may be weak due to the existence of patent protection for a medicine which is clearly the best treatment option, the threat of new competitor treatments being launched in future, i.e. of incremental innovations, is an important factor.

Like other products, a medicine's characteristics are not fully known when it appears on the market. A new medicine's value is likely to become clearer over time as it is used more, by more people, in a wider variety of circumstances. Over time, knowledge about how best to use the technology can increase and uncertainty about its value can lessen, although diffusion of new medicines in the absence of HTA does not necessarily lead to useful knowledge generation that would help boost the drug development process. This issue was discussed at some length and is covered in more detail in a later section.

An HTA body may determine in favour of accepting a medicine for reimbursement or at least accepting it for a restricted range of indications or patient groups (the majority of NICE decisions fall into the restricted category), but when an HTA body, or any other agency with a role in determining access to health technologies, makes a "not recommended" determination, this prevents 'early adoption' and *a fortiori* prevents subsequent 'imitation' in that market. The point was made in discussion that also, conversely, when an HTA body determines in favour of a medicine, users – prescribers – may feel compelled to adopt it. This element of compulsion is a peculiarity of medicines markets.

The HTA body's decision in the medicines market, whether in favour of a medicine being used or against it, is taking the place of the separate decisions of thousands or millions of individual (potential) customers in more typical markets. Consequently, the HTA body's decision criteria are crucial.

In the past it was arguably the US, private insurance dominated, market that *de facto* largely shaped innovation incentives in the pharmaceutical industry. The US represents almost half of the total value of global pharmaceutical sales and an even greater proportion than that of many pharmaceutical companies' profits. But the requirements of NICE and HTA bodies in other countries are now having an increasing influence on R&D investment, and disinvestment, decisions, and this influence is confidently expected to grow further. Furthermore, the US is now also embarking on a federally initiated programme of comparative effectiveness research.

3 The demand for pharmaceutical innovation

All Forum participants agreed that innovation is not valuable *per se* but only for what it adds to social welfare. Not all innovations will be socially valuable or worth the cost. Not all innovations carry the seeds of potential future innovations further down the path of technical progress, but some do. It was agreed in the Forum that the need is to incentivise innovation that increases social welfare, not to stimulate all innovation indiscriminately.

Better determining all of the attributes that increase social welfare, i.e. what makes society as a whole better off, is clearly a major area that would benefit from further research. Determining how to ensure that socially beneficial innovation is incentivised efficiently, however social benefit is defined, is a separate issue. The practice of HTA might reasonably be expected to serve the end of increasing social welfare. The main question for the Forum was whether and how HTA processes fit into the range of public policies and interventions aimed at ensuring efficient levels and types of socially valuable innovation.

HTA bodies might reasonably be expected to try to enable the maximisation of social welfare. This may not go as far as explicitly defining a 'social welfare function' that they try to maximise. But it is incumbent on HTA bodies to be explicit about what it is they will advise health care systems to pay for, and to honour that undertaking in the long term too so that the signal they give to (potential) private investors in R&D is credible. Forum participants agreed that there is scope for HTA bodies including NICE to be more explicit about what they include, and how, in their estimation of the value of medicines.

There is a continuing, unresolved, debate about whether HTA bodies should take the perspective of the payer for health care or adopt a rather wider societal perspective when considering the benefits and costs of a health technology. Both points of view were stated at the Forum meeting. The point was acknowledged that a societal perspective on both benefits and costs is necessary to enable resources to be allocated in a way that is most beneficial to society, but this begs many questions about how to achieve that in practice. One approach emphasises that the health system budget needs to be determined by a socially legitimate process, but that thereafter the key issue for the payer and their agents, such as NICE, is maximising the health return to that budget. An alternative approach would have NICE directly apply a broader "societal" perspective than just that of health and the tax-funded health system's budget to its appraisals of the cost-effectiveness of health technologies. (Recent discussions of societal perspective versus payer perspective arguments are in Johannesson et al., 2009, and Claxton et al., 2010).

There is plenty of scope for further research to define just what society wants to pay for and how much it is willing to pay.

Pharmaceutical R&D by one organisation may yield benefits not only in terms of improved medicines produced by it but also in "spillover" benefits to other medicines producers and even to other sectors of the economy altogether. Spillover benefits from pharmaceutical innovation appear to be of considerable magnitude (see in particular Toole, 2007, and Ward and Dranove, 1995). But there remains plenty of room for further research to assist public policy making by determining how to maximise the total social rate of return including spillovers that could be achieved by pharmaceutical R&D.

4 Should HTA processes be changed to allow for innovation path dependency?

The Forum participants agreed that innovation and dynamic efficiency are important for public policy and that HTA bodies inescapably affect them. The HTA body becomes in effect a major influence on the demand side of the market for medicines. However, even if there were a defined perspective of social welfare that is to be maximised, how could an HTA body take account in practice of the possibility that a current innovation might, or might not, be a prerequisite for some future, as yet unidentified, innovation of unknown social value – a further complication being that the company which makes the future innovation(s) may well not be the company with the current innovation.

Society may be willing to pay something today in order to keep open the option of some uncertain future benefit. Exploration of option demand in this context is perhaps warranted. But there is then a risk of double counting; of paying now for the option of future benefit and then paying again in the future (but quite possibly to a different company) if and when the benefit materialises.

Given that not all current innovations will be essential steps on the path to future, socially valuable, innovations, how could the government or an HTA body "spot the winners" for which paying a premium might be justified, and how could it determine how valuable the unknown future benefits might be and hence what magnitude of premium could justifiably be paid?

Paying for some imperfect indicator of future innovation potential would incentivise achieving that particular indicator, rather than the desired innovation itself, and thereby skew research efforts inappropriately. There is a significant risk that trying to pick areas of research to support could end up biasing research effort undesirably.

It was argued that the company producing an innovation has the best information as to its potential to lead to further future innovation, and what the benefits of that future innovation might be. While no HTA agency or any other body may have *better* information than the company, it was pointed out that companies' assessments of future markets and hence of the value of innovative products can be wildly wrong. It was suggested, for example, that companies active early in home computing and mobile telecommunications markets vastly underestimated the future scale of markets in those areas. However, this implies *a fortiori* that it would be impractical to expect an HTA agency to attempt to value future streams of benefits from as yet undeveloped innovations.

There was agreement in the Forum that the danger of paying for benefits twice ('double counting') – both in advance and when they do eventually occur (if they do, and to whomever they do) – must be avoided. The consensus was that it was preferable, as well as pragmatic, to pay for benefits only if and when they materialise and not 'on account' in advance. Therefore, in view of the major practical difficulties, the Forum participants agreed that they could not see how in practice an HTA body could adjust its decisions to allow for the possibility of currently unforeseen, path dependent, future innovation.

There is a considerable literature suggesting ways to evaluate the benefits of health care research. This literature focuses on evaluating publicly funded research but provides an interesting perspective from which to view attempts to value innovation in medicines. An up to date survey of health care research evaluation frameworks and methods is set out in the appendices to the January 2009 report of the Canadian Academy of Health Sciences (CAHS): "Making an Impact. A Preferred Framework and Indicators to Measure Returns on Investment in Health Research". One widely used method referred to there is the 'payback model' originally developed by Buxton and Hanney (1996), which uses five categories of payback to research. The CAHS report presents the five categories as follows (taken from Nason et al., 2008):

- **Knowledge production** – Journal articles, conference presentations, books, book chapters, research reports;
- **Research targeting and capacity building** – Better targeting of future research, development of research skills, personnel and overall research capacity, staff development and educational benefits;
- **Informing policy and product development** – Improved information bases for political and executive decisions, developing pharmaceutical products and therapeutic techniques;
- **Health and health sector benefits** – Improved health, cost reduction in delivering existing services, qualitative improvements in the process of delivery, improved equity in service delivery;
- **Broader economic and social benefits** – Wider economic benefits from commercial exploitation of innovations arising from R&D, economic benefits from a healthy workforce and reduction in working days lost.

The first three of these categories of potential benefits are beyond the scope of all current HTA systems. The extent to which the other two categories are taken into account varies between HTA bodies: those in Sweden and the Netherlands adopt a broader perspective than merely the costs to the health care system and the health benefits to patients, but NICE and the Scottish Medicines Consortium are required by the regulations that define their roles to take a narrower, health care payer, perspective.

The consensus among the Forum participants was that if knowledge production, improved information, better targeting of research, or development of research capacity are considered to be inadequately incentivised at present, then the solution lies with public policies to better incentivise or subsidise them directly (see examples later in this note), not with modifying HTA processes to accommodate innovation path dependency. Indeed some of those direct policies are already in place. If more knowledge or more research is wanted then that is what should be paid for. That is not a case for putting a premium on the price of any existing medicines. The Forum participants were in agreement that it was clear that the appropriate policy response, if any, was not to change HTA methods and was not the responsibility of HTA bodies.

5 Learning more about medicines and more about research

The Forum considered the important characteristic of medicines as 'experience goods'. Producers and users generally find out more about the value of a medicine, and of further developments of it, once it is on the market

and in use. A clearly expressed sentiment that was supported by a majority of the Forum participants was that we need to know more about existing drugs before we start to judge what future benefits might emerge further down the innovation path. In other words: it would be better to focus on generating more information about new products, so as to enable appropriate rewarding of value and hence to give appropriate incentive signals for future R&D, than on trying to define and reward some attribute called 'innovation'.

It is helpful at this point of the discussion to think separately of two broad types of information that are gained by studying a medicine in use, although the two types are linked. First there is the information that is gained about the particular medicine that is being used: how well it works with different groups of patients. Secondly, there is the possibility that knowledge will be gained that will stimulate or steer future research to produce as yet unknown new products. These two types of information are considered in turn in the following paragraphs.

One of the reasons why an innovative product of any kind may fail to achieve rapid take-up by the entire potential market is that when it is first launched there is uncertainty, among consumers at least, about the full range and magnitude of its characteristics: the benefits and costs associated with using it. Uncertainty is particularly likely to be an issue for innovations that are doing something fundamentally new – e.g. treating a previously untreated disease – rather than those doing something familiar but better than before.

This highlights the value of information about new medicines and other new health technologies and implies that better information and consequently reduced uncertainty should be incentivised in the HTA process. There was a lot of support from Forum participants for more and better evaluation of medicines as they are used. There is growing interest from payers in 'coverage with evidence development'. But there was no overall agreement in the Forum on the best way to evaluate medicines post-launch.

Different Forum members expressed differing degrees of willingness to accept non-trial-based observational information from monitoring the effect of using medicines post-launch without a control group for continued comparison. One perspective was that NICE and other HTA bodies should be more willing to take observational data into account, and indeed to promote its collection and evaluation. There may be a tendency currently to limit its use solely to audits of activity, rather than using it to confirm or challenge expectations of outcomes from the use of treatments and to compare those outcomes with those achieved previously with earlier treatment technologies. An opposing perspective was that only data generated from randomised controlled trials, including post-launch trials, could be relied upon.

The second type of information defined above is that which if gained could stimulate or steer future research to produce as yet unknown new products (rather than helping to maximise the benefit from using the existing medicine). This kind of information can be as valuable for what it reveals about what not to attempt, and which lines of research to curtail, as for the new research avenues it points to. What is valuable from this second perspective is the knowledge that will ultimately produce benefits, or save costs, with research that has not yet been done. The Forum participants agreed that what needs to be paid for in this case is the information itself, which does not imply paying more for the existing medicine.

6 Other ways to support efficient innovation

The Forum discussion did not cover in detail the range of specific policy options – existing and potential – for tackling any perceived shortfalls in the extent or nature of pharmaceutical innovation, but a number of such options were highlighted. They included demand-side policies other than changes to HTA processes:

- medical prize funds;
- advance market commitments;
- extensions to patent lives. Research into the trade-off between length and breadth of patent protection and impacts on innovation could be worthwile;

and on the supply side:

- tax breaks for R&D expenditure;
- selectively reducing the regulatory burden, i.e. identifying the circumstances where existing regulatory, including HTA, requirements impose unduly large cost burdens on companies;
- public provision of capital or other financial support to fund or co-fund R&D.

7 Summary

The discussion, perhaps inevitably, raised a great number of questions and highlighted many gaps or weaknesses in knowledge. But there was also a notable consensus among the participants that:

- innovation path dependency issues may exist, but certainly do not always;
- when they arise, changing HTA processes is not the most appropriate policy response;
- more fruitful would be to investigate other demand side and supply side interventions to support and encourage any areas of innovation being unduly thwarted by path dependency problems.

Underlying all three of these conclusions is a need for more research, to obtain greater understanding of:

- the nature and extent of innovation path dependency in the pharmaceutical sector in practice; and
- how companies make their R&D investment decisions in practice. Specifically we need to know just how, and how much, do payers' and HTA bodies' actions and statements actually affect companies' R&D investment decisions and activities.

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