CHAPTER 2

Health Technology Assessment (HTA) and the Incentives to Innovation in the Life Cycle of a Health Technology

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Introduction

The objective of this chapter is to explore how health technology assessment (HTA) can best be used to steer socially needed innovation in health technologies. To that end it is essential to analyse the driving factors in the life cycle of health technologies, i.e. the factors that determine how they are created, developed, regulated, used and, eventually, finally discarded, as well as the roles and motivations of the key stakeholders in this process. The next step is to design and implement the appropriate policies and institutional arrangements that provide the incentives required to ensure that the right amount and distribution of resources is applied to promote the development and use of new technologies that efficiently and equitably address existing social health needs. In order to do so, it is important to take a holistic approach that acknowledges the interactions between stakeholders and external factors in making the relevant decisions in the innovation process.

Innovation is a contentious topic, especially in the health technology sector, where availability and access to innovative treatments is a high priority for most people and sometimes a matter of life or death. In countries with universal health systems, public financing of health services removes the individual budget constraint of the consumer, making the demand for healthcare technologies very rigid, i.e. insensitive to its price. A similar phenomenon occurs in the context of voluntary and mandatory insurance systems in what is known as the *moral hazard* effect of insurance and third-party paying. As a result, the demand and supply of health technology innovations has grown steadily over time in spite of the increasingly higher prices, while the benefits of innovations in terms of health improvements to the users do not seem to grow at the same rate. To the frequently posed question "Has technological change in medicine been worth what it costs?" Garber [1] suggests that in most industries, the market would answer the question. "If too few consumers believe that a new detergent, toaster, or television is 'worth it', it will fail. But a medical product or service can succeed even if it is worth only a fraction of its cost that insured patients pay out of pocket". This is because healthcare often is either free or highly subsidised for the consumer at the time of delivery.

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Societies positively value the overall effects that the evolution of health technology has had on health and wellbeing and expect R&D to bring new treatment options for diseases that still have no cure, as well as improvements in existing treatments. On the other hand, the introduction of new health technologies is regularly blamed for being one of the main causes of the rise in health expenditure. The problem for society, and more specifically for health system managers and policy makers therefore, is to promote innovation, while at the same time ensuring the value for money of new technologies and of health expenditure, in general, and ultimately the financial sustainability of the health system. HTA certainly has a key role to play to this end, namely to provide the information required for decision makers to take the right decisions in order to promote the right type and amount of innovation in health technology.

But before trying to find out how to best promote innovation in health technology it is necessary to clarify what this term means.

The Meaning of Innovation

Innovation is a value-loaded term. In the economic literature innovation is assumed to be a key driver of productivity and economic development; innovation is hence associated with progress and prosperity, two concepts that most people value as positive and desirable. The economist Joseph Schumpeter [2] has been one of the most influential authors in the analysis of innovation and its effect on economic development. Interestingly, his central concept of "creative destruction", the process by which new technologies entering the market make the older ones obsolete or redundant, highlights the point that innovation often has negative effects as well, as it renders valueless the tangible and intangible assets on which the substituted technologies worked.

Innovation has been defined as the "successful introduction of something new and useful, for example, introducing new methods, techniques, or practices or new or altered products and services"[1]. This definition is however very vague and does not have a precise meaning, either in the technical or in the common language. Innovation is a complex, multifaceted and elusive concept that deserves a close analysis and discussion in order to fine-tune its meaning for analytical purposes.

The *Oslo Manual Guidelines for Collecting and Interpreting Innovation* is one of the key references in the analysis of innovation [3][2]. The main purpose of the Oslo manual is to provide a framework with standardised definitions and methods to measure and collect information on innovation in a rigorous and comparable way.

The Oslo manual states that "An innovation is the implementation of a new or significantly improved product (good or service) or process, a new marketing method, or a new organisational method in business practices, workplace organisation or external relations". It goes on to define four broad types of innovations: 1) product innovations[3], 2) process innovations, 3) organisational innovations and 4) marketing innovations.

1 http://en.wikipedia.org/wiki/Innovation.

2 The first edition of the manual was issued in 1992 and the second edition in 1977.

3 The development of a new use for a product is also included in the definition of product innovation.

How is innovation related to invention and to research? Innovation and invention are distinct things. An invention is a technical solution to a need or problem. In order to become an innovation, an invention has to be put into practice or implemented: in the case of products it must be introduced to the market, i.e. a manufacturer has to turn the invention into a final consumer product and produce it at a cost that is attractive for consumers to buy a large enough volume that makes production profitable and feasible; consumers – or third-party payers – have to be convinced that the innovation is effective and justifies the price they are asked to pay for it; otherwise the would-be innovation will end up in a museum of failed inventions. In the other categories – process, organisational and marketing innovations – they must be given actual use in the firm.

Research and development (R&D) defines the set of activities carried out by companies that intend to innovate. R&D often is a requirement for inventions, but a large volume of expenditure in R&D does not guarantee that inventions will follow or that inventions will find their way into the market and become commercially successful products. On the other hand, a brilliant simple idea that took little time and cost to formulate and develop, may become a breakthrough and bring large revenues to the smart innovator.

An authoritative source of definitions and analysis relevant to the topic of R&D is the Frascati manual, *The Measurement of Scientific and Technological Activities Proposed Standard Practice for Surveys on Research and Experimental Development* [4] a piece of work with a similar purpose and approach to the Oslo manual in its specific field. The Frascati manual states that "Research and experimental development (R&D) comprises creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society, and the use of this stock of knowledge to devise new applications" and indicates that R&D – both intramural (in-house) or extramural (acquired) – is only an input to the process of innovation.

What is Innovation in Health Technology?

As could be expected, innovation is by no means a univocal concept in the context of health technologies any more than in other areas of technology. Neither the Oslo, nor the Frascati manuals pay much specific attention to the health sector[4]. They nevertheless make some relevant and interesting remarks. The Oslo manual highlights, for instance, that in the services sector – which includes healthcare – production and consumption occur simultaneously and the distinction between product and process is often blurred. This remark applies to medical services and procedures, but not to medicines and other health products: they are obviously not being produced and consumed simultaneously. In the case of medicines, the so-called innovative firms seem to concentrate on developing new, more effective medicines, with limited concern for improving the production processes and reducing their cost. This is probably due to the limited impact that direct

4 The Frascati manual does not address many health-specific issues, except for some remarks on clinical trials. After mentioning the four standard phases of clinical research, it states that for the purposes of international comparison, by convention, clinical trial phases 1, 2 and 3 – which take place before permission to manufacture is accorded – can be treated as R&D, while phase 4 clinical trials, which continue testing the drug or treatment after approval and manufacture, should only be treated as R&D if they bring about a further scientific or technological advance.

manufacturing costs have on the total costs of the industry in relation to R&D, marketing and other general expenses. Reducing the manufacturing cost seems to be mainly a task for the generics industry, which is forced to do so in order to make its way in a market environment characterised by aggressive price competition.

The analysis of innovation might be better addressed if the concept can be properly contextualised and more narrowly defined and restricted in its content, for instance, if we restrict the analysis to innovation in health products (medicines and devices), rather than to the broader range of health technologies that are included under the standard definition, i.e. to entities such as medical equipment, surgical treatments, public health programmes, etc.

In order to facilitate our task, we will restrict our analysis to medical products, such as medicines, diagnostic tests, medical devices and the like. It must however be noted that in spite of its similarities, the feasibility and actual practice of technology assessment varies remarkably across medical products. Huot et al. [5] aimed to ascertain the level of evidence available for implantable medical devices (IMDs) access to reimbursement in France and concluded that IMDs are far less investigated than drugs. In the USA the situation is similar: Feldman et al. [6] state: "This drug/device split in testing extends throughout the healthcare system to health plans and hospitals, as formulary committees for drug coverage have few device-coverage correlates". The authors urge independent HTA organisations and other stakeholders to address this situation and support HTA of medical devices. There does not seem to be theoretical justification for the less frequent evaluation of health devices in relation to medicines, but rather practical and historical reasons. As mentioned above, the early occurrence of some fatal episodes in the consumption of unsafe medicines prompted a reaction in the form of conditioning market entry to the requirement of submitting evidence of safety based on clinical trials, the oldest form of HTA, and the generalisation of drug regulatory agencies in most countries, which, until recently, did not address the need to request a similar control of other medical products. Moreover, the methodology of randomised clinical trials (RCTs) has been developed for medicines and is less appropriate for medical devices and other health products.

Van Nooten et al. [7], while acknowledging that payers are increasingly interested in innovative products, recognise that definitions of "innovation" vary among stakeholders, but it can generally be defined as improvement in relative efficacy and/or efficiency compared with the current standard of care[5]. This means that innovation could be measured as an improvement in efficacy, and hence in any indicator of health outcome, such as, diseases averted, life-years gained or increase in life expectancy; total quality-adjusted life-year (QALYs) gained could be a general indicator of innovation in absolute terms, which could be standardised by cost in the form of the compound indicator "QALYs gained per additional dollar spent on a new technology". Such an indicator would recognise the time-related nature of innovation, as it would measure the improvement it meant at the time the technology was introduced, irrespective of whether it was later overcome and made obsolete by the next technology.

5 However, in the same article the authors seem to adhere to another definition of innovation, when they state that a "valuable innovation" is defined as something that "truly fills an unmet need"; they also mention that according to NICE in the UK "an innovative product is one that is new, offers an improvement compared with existing therapies and provides "a step-change in terms of outcomes for patients". In fact, all these definitions reflect quite different criteria.

The Kennedy Report's [8] main target was to assess whether other factors than the cost per QALY framework and the related threshold criterion should inform National Institute for Health and Care Excellence (NICE) decisions, particularly, whether innovation-related benefits should be considered. Kennedy made 25 recommendations, several of them specific to the issue of innovation. One of the recommendations was that NICE should establish an explicit definition for innovation in the context of health technologies (specifically, for pharmaceutical products). As Green [9] ironically commented, "Kennedy found that whilst everyone was content to use the word "innovation" and everyone agreed it was a good thing (referring to the consultation process), it was not easy to identify what was being discussed". Kennedy accepted NICE's view that innovation is supposed to meet three criteria: a) novelty, b) improvement over existing interventions, and c) providing a "step change in terms of outcomes to patients".

He went further to suggest that NICE consider the following as being possible criteria of a "step-change", and of the need for properly articulated criteria to recognise this value:

- The product significantly and substantially improves the way that a current need (including supportive care) is met
- The need met is one which the National Health Service (NHS) has identified as being important
- Where appropriate, research on stratification … has identified the population(s) in which the product is effective
- The product has been shown to have an appropriate level of effectiveness – for example, benefiting 70% of the intended target group. This may be all of the population with the condition or just a subset, and
- The product has marketing authorisation for the particular indication.

The Kennedy report globally supported the general framework used by NICE as the best tool available, but stated a certain lack of transparency in the way social value judgements were considered in the decision-making process.

He also mentioned that the contribution of the pharmaceutical industry to the wider UK economy should also be somehow considered.

The response by NICE did not suggest that likely dramatic changes would follow, in the way of making the innovation criteria more explicit, but rather that NICE would use flexibility and discretion to accommodate new relevant criteria into the incremental cost-effectiveness ratio (ICER)/QALY approach[6].

Finally it is worth presenting here the results of an exercise carried out in the context of the EU Pharmaceutical Forum meetings. Pricing and reimbursement officials from EU member states were asked to identify the types of benefits they would consider worth paying for a new medicine: "This report is a bottom-up exercise, based on discussions and collection of views from the relevant member state authorities on how to recognise, assess and reward valuable innovative medicines. This exercise covers valuable innovation in

6 NICE response to Sir Ian Kennedy's report: Appraising the value of innovation. http://www.nice.org.uk/aboutnice/howwework/researchanddevelopment/KennedyStudyNICEResponse.jsp.

three main areas: 1) therapeutic/clinical benefits regarding the disease, 2) quality-of-life benefits for the patient, and 3) broader socio-economic benefits. The table below summarises the results of the exercise."

Table 2-1. Potential benefits from innovative medicines.

Therapeutic/Clinical	Quality of Life	Socio-economic
Higher probability of full recovery	Higher physical self-sustainability/ self-management at home	Avoiding pandemics (vaccination, ...)
Faster partial or total recovery	Higher psychological self-sustainability	Dealing with resistance (HIV, antibiotics, ...)
Slower progression of diseases	Higher social self-sustainability	Reduced total cost of medication
Increased ability to cope with disease symptoms (e.g. analgesic)	Higher convenience/comfort for the patien and his environment	Reduced total cost of treatment
Higher probability of preventing the (re-)emergence of a disease		Reduced non-healthcare spending
Survival rate, life expectancy		Reduced cost of sick-leave
Fewer or less severe side effects		Higher productivity of the citizen
Fewer or less severe interactions with other medicines		
Higher tolerability		
Broader/easier dosing, improving compliance		
Easier administration schedule, improving compliance		

Source: European Commission, Enterprise and Industry. Working Group on Pricing and Reimbursement, Characterisation of the Value of Innovative Medicines [10]. © European Union, 1995–2014.

Aggregate innovation has been usually approximated by intermediate indicators, such as number of patents granted, number of new chemical entities (NCE) registered, etc. For instance, in trying to assess the assumed superiority of the US over the EU in pharmaceutical innovation claimed by Grabowsky & Wang [11], Light [12] reanalyses a set of aggregate indicators of research productivity proposed by the former, that basically rely on the number of NCEs that are classified as 1) global[7], 2) first-in-class, 3) biotech, and 4) orphan. Such indicators are not very valid and sensitive, as they assume that all NCEs are innovative and homogenous, i.e. that they have the same innovative value. This certainly is a strong assumption that makes them useless to assess the degree of therapeutic innovation of single medicines. The number of patents granted is also taken by some authors as an indicator of the degree of innovative activity. But similar to the variable "NCEs marketed",

7 Global was defined according to various criteria: introduced into four or more of the G7 (Group of 7) countries.

patents are not unambiguously associated with therapeutic advances. A larger number of patents might just mean that innovators are more likely to submit patent applications, or that patent offices maintain lower patentability requirements for granting a patent. Finally, patents are as heterogeneous as NCEs as indicators of the degree of innovation.

Motola et al. [13] developed an algorithm to assess the degree of therapeutic innovation of new therapeutic agents by evaluating a) the seriousness of the disease, b) the availability of previous treatments, and c) the extent of the therapeutic effect. The combination of these three variables yielded three scores of therapeutic innovation: A, important, B, moderate and C, modest.

The authors applied this score to all medicinal products approved by the European Medicines Agency (EMA) between January 1995 and June 2003, and later [14] to the products approved between January 1995 and July 2004; the second study included 227 medicinal products corresponding to 209 active substances. Among all therapeutic agents, only 28% were classified in category A, although most of the substances were claimed as innovative by the respective manufacturers.

As in any other domain or field of technology, there are diverging interpretations of the meaning of innovation and of the way to assess and measure it: right holders and producers usually pretend that any new product or procedure that is different from existing ones is an innovation, quite irrespective of how it works and of the contribution it makes to health outcomes. However, innovation is increasingly defined in the healthcare sector as added value, which is generally identified with therapeutic added-value or utility, i.e. a health innovation would be any new technology or new application of an existing technology that provides a better health outcome than existing technologies in the same application.

Morgan et al. [15] found that between 1996 and 2003 the Patented Medicines Pricing Review Board (PMPRB) of Canada classified 68 (5.9%) of the new products as "breakthroughs", while for the remaining 1005 new products, the PMPRB did not find any evidence of therapeutic advantage over existing treatments and were classified as "me-toos". The result was that the share of "me-toos" increased from 41% in 1996 to almost two-thirds in 2003, accounting for about 80% of the increase in expenditure, which seems a high price for society to pay for the social benefit added by these drugs.

Innovation may also have detrimental effects for the consumers, due, for instance, to the occurrence of unexpected or hidden negative effects. A recent analysis of the Canadian market [16] showed that of the 528 new drugs approved in Canada between January 1990 and December 2009, a total of 22 (4.4%) were withdrawn for safety reasons until October 2013. The median time to withdrawal was 1271 days, which according to the author "emphasizes the need to be particularly cautious in prescribing new drugs early in their life cycle".

If only health benefits for the patient are considered, innovation could be defined and measured as a health gain, by means of a measure of health such as the QALYs; whereas, if changes in resource use and other effects are to be included in the impact, innovation could be measured by an improvement in the net social benefit. In both cases innovation should be measured against the most effective or the most efficient existing technology, respectively, and be preferably standardised by its additional costs.

Anyway, even if we could agree on a general definition of innovation in terms of added value, it is obvious that the precise content of this term is subjective and dependent on each individual's values and perceptions. The long debate between welfarists and extra-

welfarists is proof of the subjectivity of the issue, which cannot be solved with exclusive recourse to objective and scientific arguments: all we can expect is to reach increasingly larger consensus in value judgements.

Definitions of innovation might be unclear, and inconsistent across laws, regulations and policies, but the request for demonstrating evidence of product innovation is likely to rise in the future as a condition for a medical product to attain market access and premium pricing.

Key Decisions in the Life Cycle of Health Technologies: Do the Present Institutional Arrangements Provide Appropriate Incentives for Socially Needed Innovation?

Innovators must take multiple decisions along the life cycle of a health technology. Some decisions are of a scientific or technological nature and are related to the R&D process itself. Other decisions are related to the institutional, economic and legal aspects of the product development and marketing[8].

First the innovator must select the objective of his innovative activity. It might decide to advance its own resources, or look for either public or philanthropic funding to develop its own idea[9]. It can also apply for philanthropic or public funds, which are earmarked for a given innovation selected by the funding organisation.

Later in the life cycle of the innovation it will have to decide whether, when, where and how to look for intellectual property (IP) protection, which type of claim to make (broad or narrow), etc.

When the invention is ready for consumer use, the innovator might have to obtain a marketing authorisation. Obtaining a marketing authorisation[10] is a necessary step for a medicine to legally enter the market in most countries. Again, the innovator will have to decide when and where to make a submission, for which indications, specify conditions or restrictions of use (e.g. hospital use only), etc.

The role of publicly funded research & development

Publicly financed R&D usually concentrates on basic research, but it does also address clinical research. A debate has been going on with inconclusive results on the complementarity of public and private research. Toole [17] found strong evidence that "public basic and clinic research are complementary to pharmaceutical R&D investment and thereby stimulate private-industry investment". The influence of public research is determined by the degree to which industry scientists draw from and add to public scientific knowledge. Basic research opens new lines to therapeutic outcomes by accepting a high degree of uncertainty in the feasibility of obtaining results and on its likely market applicability. It has also been suggested that publicly financed research

8 The following list of questions does not pretend to be exhaustive, but only illustrative of some of the main decisions the average innovator will face.

9 An intermediate option is to look for partial grants and subsidies or tax breaks.

10 Also referred to as licensing or registration.

plays an important role in finding new applications for older, off-patent drugs. In a posterior article Toole [18] found that public basic research has its main impact in the earliest part of the drug discovery stage of industry research, the concept phase. He concludes that the investment in basic research by the National Institutes of Health (NIH) influence pharmaceutical innovation 14 to 20 years prior to the drug application and that a 10% increase in public investment in basic research leads to a 6.4% increase in the number of drugs in the market.

The World Health Organization (WHO) has been supporting meetings and debates for several years in order to explore mechanisms to improve coordination in research for neglected diseases and more specifically, to explore interventions that delink the cost of R&D from final price in order to improve affordability.

"A Consultative Expert Working Group on R&D Coordination and Financing (CEWG) was established to analyse various proposals for innovative mechanisms. The WHO working group through a process of public consultations has received various proposals from WHO member states, civil society, academics, industry and other stakeholders. Proposals that have been considered include: innovation inducement prizes (both prizes for final products as well as milestone prizes); open source R&D models; priority review vouchers; new indirect taxes; medicines patent pools; equitable and humanitarian licenses; biomedical R&D treaty; pooled funds related proposals; advanced market commitments, Health Impact Fund, Green Intellectual Property." After a hotly debated process of selection, the 67th World Assembly in May 2014 considered the following proposals: a global R&D and access initiative for visceral leishmaniasis by the Drugs for Neglected Diseases *initiative* (DNDi); an international open-source collaboration to accelerate drug development in addressing diseases of poverty by the Medicines for Malaria Venture (MMV); and the development of easy to use and affordable biomarkers as diagnostics for the neglected tropical diseases by the African Network for Drugs and Diagnostics Innovation (ANDI). Finally the Special Programme for Research & Training in Tropical Diseases (TDR) suggested the creation of a new pooling funding mechanism.

Patents and other exclusivity rights

Patents, intellectual property rights (IPR) and other exclusivity rights provide financial incentives – a potential monopoly – to rights holders. They allow the appropriation by the innovator of the commercial value of the innovation market demand, by selling either a) the IPR itself, b) voluntary licenses, or c) the final products, which, thanks to market exclusivity, can be sold at higher prices than under competition and allow for extraordinary profits.

IPR always had strong critics, the earliest ones being the most liberal, pro-market economists, who found IPR were in conflict with the principles of competition. Criticisms to the present patent system ranges from technical topics that the authors think can be fixed with reforms that do not essentially question the principles and main practices of the system (Federal Trade Commission, 2003), to authors who ask for deeper reforms [19] up to those who claim that the system is "broke" and think that it requires radical changes [20].

The more radical approaches claim that a reward is needed for innovation, but not necessarily the present type of patents and other types of monopolistic, exclusive marketing rights, such as test data protection, which allow the right holder to exclude potential competitors and lead to high prices that make medicines unaffordable for a large part of the population. Property rights could take the form of a fixed royalty, or a right to a defined amount of money. Lexchin [12] claims that there is enough evidence to state that lower prices would not necessarily jeopardise drug research.

Licensing

Licensing, also known as registration or marketing authorisation, is the first institutional test hurdle, according to industry, that a drug has to overcome in its life cycle in most countries. However, it does not pose very strict requirements in relation to efficacy, as regulators usually grant the licensing of new drugs if they show either non-inferiority to an existing one or superiority to placebo. None of these two alternative criteria ensure that the licensed drug brings a therapeutic added value. Moreover, the weak transparency requirements on the results of clinical trials have for many years allowed clinical trials to be simply withdrawn when the results were not favourable (enough) for the new product. Together with the lack of a requirement for standardised reporting and transparent and comprehensive disclosure of trial results – often in the name of patient confidentiality and other fundamental rights – they question the validity of any systematic review of the evidence based on RCTs. If researchers do not have access to all the clinical trials that involve a given product, there is no way to guarantee that the most systematic literature reviews and meta-analyses will yield valid, unbiased and reliable aggregate results.

Pricing and financing

Pricing systems are increasingly aimed at rewarding therapeutic added value. It is becoming customary not to accept a premium price for a new drug over that of existing alternatives unless the new drug can provide evidence of adding some therapeutic advantage or added value to the existing treatments, what is generically known as value-based pricing. As Rai [21] indicates, "the use of QALY based analysis by payors is an indirect mechanism for channelling biomedical innovation in a direction that maximises QALY" that "does not involve intellectual (IP) policy per se at all". Although the use of value-based pricing indirectly involves IP policy[11], the author is right when he states that "A more IP-based approach to maximising QALY might involve a patent prize system that calibrated rewards based on the number of QALYs produced by the technology" [21].

VBP uses HTA to address the conflict between setting prices low enough to be affordable and high enough to incentivise companies to develop new, effective treatments and signalling the companies that society is willing to pay for good value, i.e. innovative pharmaceuticals.

11 Because it is precisely the market power granted by patents and other exclusivity rights allows the regulator to steer the incentives of innovators by allowing market power to materialise in certain directions.

Options and Proposals for Using Health Technology Assessment to Assist Policy Practices Aimed at Promoting Socially Needed Innovation in Health

Several authoritative sources have expressed their concerns about the capacity of the market to efficiently allocate resources to innovation in health. The reasons are manifold: the diverging interests of innovators – especially commercial ones, on one hand, and health systems and society at large, on the other; lack of adequate information to consumers and their agents (health professionals); moral hazard; externalities; and above all, the market failure of biomedical knowledge and information being global public goods.

The Kennedy report highlighted that there is an inevitable conflict between individual interests (e.g. pharmaceutical industry interests) and the perspective of NICE, which is concerned with the collective needs of all patients [9]. Adang [22] also points to the obvious conflicts of interest at stake: "The firm adheres to the firm perspective, which is maximising shareholders' wealth by following the net present value rule (choosing those projects with the highest net present value). CEAs in healthcare usually follow a societal perspective maximising societal health using the incremental cost per quality-adjusted life years rule." It is not clear how the imperfect health markets can reconcile these conflicting positions in selecting objectives and allocating resources to innovation.

It is therefore legitimate and relevant to analyse the way the present innovation processes operate, how far and efficiently they satisfy society's innovation needs (or desires) and whether and how changes can be introduced to improve the said processes. Some authors have reviewed and summarised the proposed alternatives to the present system of incentives to medical innovation. Nathan [23] and Rovira [24] provide global overviews of proposals and suggestions for improving the impact of pharmaceutical research, development and utilisation on global medical need; Mueller-Langer [25] makes a similar exercise but focusing specifically on neglected infectious diseases.

The role of health technology assessment as a tool for efficiently promoting innovation

HTA has been proposed as a tool to improve the relevance of future research by identifying gaps in evidence and improving research design. One way to attain this goal is to meaningfully involve all relevant stakeholders (patients, clinicians and payers) in the process of defining future research needs and designing studies to address these needs [26].

Ladabaum [27] suggests that by assessing the relative clinical value of interventions we could unleash market forces to develop the kind of cost-saving innovations that have been typical in other industries, but rare in healthcare. But providing information in itself might not lead to a change of behaviour if there are no incentives – financial or otherwise – to do so.

Health technology assessment in public funding of research & development

Funding biomedical R&D would certainly benefit from some form of priority setting among disease areas. Cost and burden of disease studies can provide a first approximation to the social need and to potential social benefits of R&D and innovation by disease

or disease area. QALYs or disability-adjusted life-years (DALYs) lost due to premature – i.e. potentially avoidable – mortality and morbidity can be weighted by other criteria to account for social values or preferences for certain conditions – rare diseases, children's diseases, unavailability of treatment, end of life or life-threatening conditions, etc., – could be allocated a higher weight if these are society's preferences.

Of course, the choice of disease and of specific health problem for R&D should not take into account only the potential benefits of finding a solution, but also of the likely additional effort required to reach the solution. Moreover, an integral view of the problem should take into account not only the estimated costs of finding the solution, but also the estimated cost of providing it to those in need. In practice however, it might be difficult to make even rough credible estimates of any of these future costs. But making these estimates and taking the respective risks is anyway part of the task of innovators and policy makers. The need for an integrated incentives policy has become evident in the field of rare diseases. Companies receive substantial public subsidies to R&D in orphan drugs, but health authorities often do not reimburse later the new drugs because they feel the price is too high; if the product is not reimbursed, the subsidies to R&D turn out to be a waste! It would probably make more sense to jointly negotiate the subsidies to R&D and the future price of the expected drug – as a package of public financing – and condition the subsidies to R&D to a previous agreement on the price of the product.

Health technology assessment by innovators during the process of research & development

Innovators are increasingly requested by payers to prove not only safety and efficacy, but also effectiveness, relative effectiveness and cost effectiveness of their products in order to get reimbursed at a favourable price. For innovator companies it has become a current practice to develop effectiveness and economic evaluation studies as a complement of its clinical research programme. Initially, these studies were done independently from the clinical research programme, often when the indications and even the price of the new product had been already decided. Economic evaluations were considered part of the marketing of a new product. But it later became clear that it was more efficient to plan real world and economic evaluation studies simultaneously and in coordination with the clinical research programme. One should expect that innovator companies progressively start the cost-effectiveness assessments at an earlier phase of the product development and that the early estimates of the cost effectiveness of products on the R&D pipeline increasingly become a criterion for continuing or dropping the development process of a product.

Health technology assessment and intellectual property rights policies

One of the traits of patents in the case of medicines is that they are granted at an early stage of the life cycle of a technology, when there is little or no evidence on the safety and efficacy and much less on the effectiveness of the new product[12]. As a consequence, from the point of view of patent law, innovation in the field of health technologies has little to do

12 This is done in order to prevent that relevant information is disclosed to other parties before the invention is duly protected.

with the concept of added therapeutic value, a criterion that is however increasingly used at the pricing and reimbursement phases. The patent holder is given an exclusivity right, which often amounts to an actual monopoly, on a product that might not bring to the patients any benefit over existing treatments. Moreover, there is a strong asymmetry of information that allows the patent holder to market the product with an aura of superiority over existing products. One way to overcome this undesirable situation would be to turn the patent right into a provisional exclusivity right that would be confirmed at the time of registration only if the patent holder could provide evidence of relative effectiveness or added therapeutic value over the most effective product existing at the time the patent was submitted. In case the added value could not be shown, the innovator would still be allowed to market the product, but not under exclusivity. A similar approach would be to modulate the patent duration according to the degree of innovation estimated through HTA studies at the time of licensing.

Several authors have proposed a flexible drug patent term as a mechanism to stimulate innovation and health [28]. This option might address the problems of the uncertainty on the future benefits of a new drug at the time the patents are granted and the convenience of being able to provide different financial stimulus for different degrees of innovation. However, it is not clear that modulating the patent term has any theoretical or practical advantage over the use of pricing and reimbursement policies as a means to attain the said objective, i.e. to reward the innovator according to the added value of the innovation.

HTA could also be used to determine the royalty paid to the patent holder in case of compulsory licensing (CL). Patent laws usually state that a fair compensation has to be paid to the patent holder, but they do not specify the criteria to calculate the amount of the compensation or royalty and leave this decision to the courts. Should a fair and efficient compensation not be somehow proportional to the added value of the innovation that is the target of a CL?

Other authors support the idea that in some cases the government should buy the patents and make them available to manufacturers in order to reduce the price and improve accessibility [29]. Again, setting a fair price for a patent is not an easy exercise, but it would probably make sense that it had some relationship to the benefits of the product concerned, no doubt a task for HTA.

Under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, countries are free to define innovation almost as they like. Most countries do not identify innovation in health with therapeutic added value or relative effectiveness. One interesting exception is India, and example that shows that a country can use its right – accepted under TRIPS – to define innovation, to protect their national interests. Section 3 (d) of India's patent law prohibits granting patents to new forms of known substances unless it results in enhanced efficacy over the known substance. Under this provision, Novartis lost protection on its blockbuster drug Glivec® last year and recently the Indian Patent Office has refused a patent on US firm Abraxis BioSciences' anti-cancer drug Abraxane®, paving the way for domestic companies to launch affordable versions in the local market. The application was refused on the grounds of the US firm's claims lacking of inventive step, not being patentable and insufficiency, legal sources say[13].

13 According to a story of the *Times of India* quoted in IP-health by James Love on June 24, 2014.

Prizes and health innovation funds

A new idea that has been proposed to substitute or complement the incentives provided by patents is paying directly for innovation instead of granting innovators the privilege of exclusivity, which often becomes a monopoly. Once the innovation is adequately rewarded it would become public domain and the final products (medicines and other health goods) would be produced under competitive conditions, as generics.

This approach is usually referred to as delinking. Incentives for innovation from prizes, implies the separation of the innovation and the products markets [30]. The rationale behind that approach is that research-based pharmaceutical companies carry out two separate activities, namely R&D and manufacturing medicines. Under the present IPR system there is only one form of rewarding the two activities: the sale of the final products. A prize system would allow to pay independently for the two activities and to avoid the problems associated with the monopolisation of the product market and the deadweight loss of monopolies.

Stiglitz [31] is one of the best known economists who advocates the use of prizes instead of IPR to promote pharmaceutical innovation. While acknowledging that innovation is at the heart of the success of a modern economy, he raises the question of how best to promote it, pointing at the negative effects of IPR and claiming that "TRIPS imposed a system that was not optimally designed for an advanced industrial country, but was even more poorly suited to a poor country". He proposes a prize fund paid for by industrialised nations that "would provide large prizes for cures and vaccines for diseases such as AIDS and malaria that affect millions of people". In his opinion this would provide appropriate incentives for research without the inefficiencies associated with monopolisation.

But the person who has more intensively lobbied for alternative non-monopolistic mechanisms to incentivise innovation in the biomedical field and has been more influential with his proposals of prizes, health innovation funds and an International Treaty for Financing Biomedical Research certainly is James Love, director of Knowledge Ecology International[14] [32]. The idea behind a health innovation fund is that all innovators would register their innovations at a certain office, but instead of an exclusivity right, they would receive a right to a part of the fund, which would be proportional to some measure of the benefits of the innovation (e.g. total QALYs gained or total net benefit). Each innovation is allocated an individual score (e.g. based on cost-effectiveness criteria) and will receive a reward from the fund over a number of years. The points accumulated by the innovation in a given year are the cost-effectiveness score times the number of treatments consumed in the year. The annual fund is distributed among innovators according to the points (scores) accumulated during the year by the products introduced in the current or in the previous X years. Such a fund turns out to be a fixed prospective budget for innovation.

HTA would certainly have a key role to play in this new approach, either in assessing the maximum appropriate amount for a prize according to a willingness to pay (WTP) estimation or in calculating the innovation scores to apportion the annual health innovation fund compensation among all entitled innovations. Hollis [33] made a concrete proposal for the creation of a fund for pharmaceutical research where the prizes are determined with the help of economic evaluation analyses.

14 See, http://keionline.org.

Health technology assessment in licensing medicines and other health products

HTA – basically, RTCs – is already used at present for licensing medicines. The questions under discussion are whether a) the assessment and the decision to authorise the product should be more restrictive, by requesting evidence of superiority – or at least, non-inferiority – over the most effective alternative available, and b) the same criterion should be extended and generalised to other, or to all health products and technologies; Feldman et al. [6] urged independent HTA organisations and other stakeholders to address this apparently anomalous situation and support HTA of medical devices.

The possibility of requesting comparison and superiority of existing treatments in order to grant a marketing authorisation might have a risk, namely that of "killing" potentially useful new products that cannot provide evidence of superiority at the time of licensing, but could attain it later through the learning process involved in its use in clinical practice. Theoretically, this risk could be reduced by some form of initial controlled or conditional use scheme, such as a risk-sharing agreement or a patient access scheme. But the problem is that once a new technology is licensed, it might become politically difficult to stop or control the diffusion, even if evidence shows later that it is clearly not cost effective, nor even effective[15].

Ben Goldacre [34], a practising doctor, wrote an angry article to *The Guardian* expressing his frustration with the way he was misled by the partial information he had received on the effects of reboxetine. He concludes: "Drugs are tested by the people who manufacture them, in poorly designed trials, on hopelessly small numbers of weird, unrepresentative patients, and analysed using techniques that are flawed by design, in such a way that they exaggerate the benefits of treatments. Unsurprisingly, these trials tend to produce results that favour the manufacturer. When trials throw up results that companies don't like, they are perfectly entitled to hide them from doctors and patients, so we only ever see a distorted picture of any drug's true effects. Regulators see most of the trial data, but only from early on in a drug's life, and even then they don't give these data to doctors or patients, or even to other parts of government. This distorted evidence is then communicated and applied in a distorted fashion."

In the first months of 2014 there have been important initiatives at the EU level in favour of improving the transparency of clinical trials, which has been supported by strong citizen pressure; now EU member states have to negotiate the final text with Parliament. There is a Parliament opinion that post-market authorisation clinical trial data should be public, but Big Pharma is lobbying against it on the grounds of commercial confidentiality[16].

Health technology assessment in pricing and financing health products

Relative effectiveness and cost effectiveness are two key criteria increasingly requested as part of the procedures for the adoption, financing and pricing of the technologies. In fact, here is where HTA is more used at present to ensure the effectiveness and cost ef-

15 If the technology is in the market, and the innovator aggressively advertises and promotes its use, it might be difficult to keep it outside public reimbursement and/or to force a cost-effective reduction of the price, especially in countries where HTA is not well established.

16 Clinical Trial Vote: the good, the bad, the uncertain, Posted by David in uncategorised, http://tacd-ip.org/archives/date/2013/05

fectiveness of the new technologies and where it does simultaneously serve to incentivise innovation: if potential innovators consistently observe that authorities are more likely to adopt, reimburse and accept a relatively high price or a price premium over existing alternatives to technologies which are able to show added value according to transparent and predictable methods, they get a clear signal of the type of innovation the health system and regulators are prepared to pay for.

Pricing based on economic evaluations with some explicit or implicit threshold to somehow define the criterion for reimbursement or refusal of new medicines and other health technologies has been increasingly applied since the early 1990s in Australia, Ontario (Canada), the UK, the Netherlands, Sweden and other countries. This approach, with some variations and modalities, has come to be known now as value base pricing (VBP). NICE is one of the clearer and most transparent examples of this approach, and it has issued guidance to approve the routine use of a health intervention, reject it or recommend use within a research programme [35]. NICE has also established a formal process for the consideration of patient access schemes (PASS), which aims at linking access to improving cost effectiveness with evidence generated after licensing. Reimbursement decisions are linked with recommendations for further research, meaning that HTA is clearly influencing – or at least trying to influence – innovation.

VBP has been practised too in Sweden for patent-protected drugs since 2002. The system attempts to set prices on the perceived value, rather than on the "actual cost". The authors of a recent article [36] claim, however, that the system can be improved, by addressing its main present shortcoming, namely, "the conflict arising when the national agency makes decisions about pricing and reimbursement while the budget responsibility for drugs is with the health providers at the regional level". The modification suggested is to split the payment of medicines: the county councils would pay the marginal cost of production while the state would pay for the innovation. This proposal seems to follow the rationale of delinking the incentives for innovation from the prices of the products.

Countries that use external reference pricing (ERP) – maybe because they are not able to apply HTA and VBP – could still promote innovation by using a basket of reference countries that properly use VBP to reward innovation, and adjust the average price of those countries by means of a relative average income or PPP index.

Health technology assessment and competition policy

Innovators should be adequately rewarded for socially needed innovation. But, as long as the reward and the incentives rely on exclusive property and marketing rights, public authorities should ensure that these rights are not misused or abused. Right holders must be credibly convinced that the temporary exclusivity will effectively finish when it is due to finish. If they feel that it is feasible to extend the period or the scope of exclusivity beyond the limits set, they might probably be more interested in spending their money in trying to extend as long as possible their temporary position, than in finding new, innovative technologies. From a commercial, profit-seeking perspective, it is perfectly rational for a company to spend the money where it is likely to produce more profits. Strategies such as *evergreening*, defensive patenting, agreements with generic competitors to delay the market entry of generics, aggressive advertising and marketing to ensure brand loyalty

once the patent expires, discrediting good quality generics and many other strategies may increase corporate profits, but do not contribute to the welfare of consumers, and even though some of them are perfectly legal, these practices should be discouraged as far as possible. The competitive anomaly of marketing exclusivity should at least be effectively transitory and under control. Companies should not be allowed to abuse IPRs and modify or use IP legislation to extend monopoly/exclusivity beyond its originally intended purposes.

Conclusions

The fact that the market fails in allocating resources to innovation in health does not guarantee that regulators, experts and public officials will automatically do better. But the appropriate use of HTA can be a key tool to ensure that public decisions are as efficient as possible, given the limited information and the uncertainties that have to be faced any time a decision is taken along the life cycle of a health technology.

The procedures to measure innovation will always have a high degree of subjectivity and arbitrariness. Most actual procedures and attempts to measure innovation go along similar methodological lines and resemble the aggregate approach of Grabowsky & Wang [11] or Light [12], or the scoring system used by Motola et al. [13], which define innovation as a set of relevant dimensions, each dimension having several discrete levels. The global innovation score is computed by aggregating with a certain procedure or algorithm the values of the individual dimensions.

HTA and more specifically cost-effectiveness analysis (CEA) do indirectly influence innovation in its role as a tool to regulate the price of health products.

Recommendations

Health authorities should first define social health needs and innovation goals and priorities. Then they should identify all the participants involved in the process of health technology innovation and their respective motivations as well as the factors that influence them and all existing or potential policy tools that can be used along the life cycle of a technology, to provide the right incentives to the stakeholders. HTA can play a central role in identifying the most innovative technologies; but just knowing that a new technology is efficient might not lead to its adoption by the health system. Health authorities should use this information when designing and applying policies in the areas of funding and promoting biomedical R&D, IP, licensing, pricing and financing health products, competition policy, and so on.

Innovation should be defined and measured as the contribution of a new technology to the effects that society values in health technologies in relation to the best available therapeutic option. For purposes of adoption, pricing and reimbursement of the added value of a new technology should reflect first of all the additional therapeutic benefit to the patients and consumers; it should also consider economic benefits in the form of savings in global treatment costs, as they free resources that can be reallocated to other health or social uses. It might also consider other benefits to patients and consumers, such as convenience of administration of a treatment, as well as benefits to caregivers and relatives.

There are various mechanisms available in the present life cycle of health products that can be used to promote innovation, and other alternative mechanisms have been proposed. The main message of this essay is that HTA should be systematically incorporated in all these mechanisms, because HTA is the best analytical tool available to assess added value and, hence, steer R&D and innovation of health technology in the appropriate direction. Of course, HTA might not always be as precise as desirable from a scientific or academic perspective, but rather speculative, especially in the early stages of the technology life cycle. But even if the results of HTA are fraught with uncertainty and are less precise and reliable than one would like, they can be of great value to regulators, payors and innovators, which, even at these early phases must take decisions that affect the innovation process. A valid even if imprecise assessment at the time an R&D investment has to be made is more valuable to the policy-maker responsible for promoting innovation, and certainly to the decision-making innovator, than a highly precise HTA available when the investment required to develop the innovation has been partly or fully made and the allocation of resources is largely irreversible.

Innovations embodied in a technology that do not result in immediate benefits for society, but might facilitate them when they are used in future technologies, might also justify some type of reward, as long as they are not appropriated by the innovator by means of property rights and are open for use to all members of society. But it is not clear by whom, when and how this reward should be paid and what would be the right amount. Some form of prize to be paid *a posteriori* from a special fund for promoting innovation would be a more appropriate source of funding than a premium price to be paid by consumers or from public health budgets.

Something that should clearly be enforced in order to ensure the validity and credibility of HTA and allow the identification of the truly innovative technologies is the preregistration of RCT in public registries, coupled with the obligation of full standardised reporting of the protocols and results of the trials. The reasons are quite obvious: unless these rules are enforced, health professionals, or the scientific community or the drug regulatory authorities (DRAs) cannot be sure if they only have access to a biased sample of the existing evidence, because innovators might not disclose the existence of RCTs that give unfavourable results for the products they promote; or they can disclose the trials, but somehow hide the unfavourable results.

For DRAs it would be quite easy to enforce transparency at the licensing stage: all they have to do is to only accept as part of the submission dossiers RCTs that fulfilled the two conditions mentioned before, i.e. preregistration of the trial and full disclosure of protocol and results. Companies would be forced to comply, because otherwise non-registered trials with favourable results would not be accepted as evidence of efficacy and safety. An additional, more radical proposal to avoid the obvious conflict of interest of innovators designing and carrying out the trials for their products would be for DRA to request that at least some key trials for the licensing procedure should be done by independent organisations selected by random procedures. For instance, Baker [37] states that in order to attain the desirable level of transparency, clinical trials should be planned and financed by the public sector and carried out by entities independent from the industry.

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