
White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of York.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/3956/

Article:
McCabe, Christopher, Claxton, Karl and O'Hagan, Anthony (2008) Why licensing authorities need to consider the net value of new drugs in assigning review priorities: Addressing the tension between licensing and reimbursement. International Journal of Technology Assessment in Health Care. pp. 140-145. ISSN: 0266-4623

https://doi.org/10.1017/S0266462308080197

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.


UNIVERSITY OF LEEDS
University of Sheffield
UNIVERSITY of York

promoting access to White Rose research papers

Universities of Leeds, Sheffield and York
http://eprints.whiterose.ac.uk/

This is an author produced version of a paper published in **International Journal of Technology Assessment in Health Care.**

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/3956/

Published paper
McCabe, C. J., Claxton, K. and O'Hagan, A. (2008) *Why licensing authorities need to consider the net value of new drugs in assigning review priorities: Addressing the tension between licensing and reimbursement.* International Journal of Technology Assessment in Health Care, 24 (2). pp. 140-145.

White Rose Research Online
eprints@whiterose.ac.uk

Why licensing authorities need to consider the net value of new drugs in assigning review priorities – addressing the tension between licensing and reimbursement.

Short title: Cost effectiveness analysis and licensing

Christopher McCabe[1] Karl Claxton[2] Anthony O'Hagan[3]

1 Professor of Health Economics, Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, UK

2 Professor of Economics, Centre for Health Economics, University of York, UK

3. Professor of Probability and Statistics, Department of Probability and Statistics, University of Sheffield, UK

Abstract

Pharmaceutical regulators and health care reimbursement authorities operate in different intellectual paradigms and adopt very different decision rules. As a result drugs that have been licensed are often not available to all patients who could benefit because reimbursement authorities judge that the cost of therapies is greater than the health produced. This creates uncertainty for pharmaceutical companies planning their R&D investment, as licensing is no longer a guarantee of market access. In this paper we propose that it would be consistent with the objectives of pharmaceutical regulators to utilise the Net Benefit Framework of reimbursement authorities to identify those therapies that should be subject to priority review, that it is feasible to do so and that this would have a number of positive effects for patients, industry and health care systems.

Key words: Public Health, Licensing, Cost Effectiveness Analysis, Reimbursement

Introduction

Health care systems are struggling to pay for the newest pharmaceutical therapies; especially those produced through exploitation of the developments in biotechnology and genomics. These costs can be orders of magnitude greater than the conventional small molecule therapies. [18]

There has been a variety of responses to this problem. Some have argued that cost of developing new drugs is too high and that this threatens our ability to reap the benefit from recent advances in medical science. Others have argued that the return on investment in the pharmaceutical industry is not sustainable,[2] whilst still others have argued that these costs should be met as they are an investment in future innovation. [18]

Those responsible for managing health care budgets have designed systems which attempt to allocate resources to therapies on the basis of some assessment of the value of the health produced. [17] [15] [4] These processes have been criticised for impeding patient access to therapies which the licensing authorities have already assessed and deemed to be of value.[1]

In this paper we briefly review the evidence for the increasing influence of cost-value assessments in determining market access. We then consider the

function of the licensing authorities. Section three examines the nature of the tension between licensing and reimbursement. In section four we outline a proposal for the adoption of value-based assessment in a small but important area of licensing activity – expedited review – arguing that this would improve the ability of licensing authorities to meet their stated objectives. Section Five considers potential benefits and problems with value based licensing.

Section 2: Licensing, value assessments and market access.

Until the 1990s licensing was the sole hurdle to market access for the pharmaceutical industry. However, the last 20 years has seen the gradual development of an additional hurdle to market access. Organisations responsible for managing health care budgets increasingly require evidence on value for money. To be good value drugs have to provide health gain at a price that is deemed affordable. Canada and Australia were early pioneers of this approach; and by 2007many major markets have established processes that consider the value, or efficiency, of new drugs as part of the reimbursement decision making process. Even the United States of America, the Medicare Payment Advisory Commission is now required to consider the budgetary implications of its recommendations.[13]

As a result of these developments pharmaceutical companies are concerned about the sustainability of the return on the large investments they make in the research and development; and researchers are increasingly concerned that the public will not be able to reap the benefits of today's rapid expansion in medical knowledge.[18]

Pharmaceutical Licensing

The United States Food and Drug Administration and the European Medicines Evaluation Agency are responsible for licensing drugs for approximately 80% of the world pharmaceutical market. The stated aims of these two organisations are remarkably similar and both include the promotion of public health. [11] [12]

Interestingly, although the public health is mentioned in both mission statements – neither organisation provides a definition of what they mean by 'the public health'. The Oxford Textbook of Public Health provides the following definition:

"'Public health is the process of mobilizing and engaging local, state, national and international *resources* to assure the conditions in which people can be healthy.' (italics added). [8]

To effectively pursue the objective of promoting the public health, licensing authorities may legitimately wish to consider whether a specific 'mobilisation of resources' makes a greater or lesser contribution to people's capacity to be healthy, than an alternative 'mobilisation of resources'. Thus, consideration of what economists call opportunity cost is not inconsistent with the objectives of the licensing authorities.

Whilst consideration of opportunity cost may not be inconsistent with the licensing authorities' objectives, to date they have not done so. Licensing has operated in a consumer protection framework. Their role has been to ensure the product is safe and efficacious. The consumer decides whether the cost to them is justified by the expected health gain. However, the cost of drugs means that such individual decisions are increasingly rare. The opportunity cost implications of paying for a specific treatment are rarely confined to an individual. In systems where the health care budget is fixed, paying for new interventions displaces other treatments. Under insurance, the inclusion of a more expensive treatment increases insurance premiums and, at the margin, some individuals are squeezed out of the health care insurance market. As the cost of new drugs increases, the link between licensing in a consumer protection framework and the promotion of public health becomes increasingly tenuous.

Section 3: Licensing, reimbursement and the public health

Licensing focuses upon quality, efficacy and safety. It considers whether the benefits the therapy provides to the many outweigh the harm that it will do to a few; benefits and harms are considered in terms biochemical markers and clinical events. Such measures, with the exception of mortality, are disease specific. Thus licensing only considers the population of people with the condition for which the therapy will be licensed. It is unable to consider the benefits and harms to the total population. This is a significant constraint on its capacity to promote public health, as it cannot compare the population health implications of prioritising the licensing of one therapy or another.

There is a perception that reimbursement processes are fundamentally different to licensing processes. However, both share the central principle of balancing the benefits and the harms in deciding whether it should be made available. The difference between them is in the scope of benefits and harm, and the population they consider. Reimbursement authorities increasingly recognise that when resources are limited, one of the harms associated with providing a therapy for one person is the opportunities for health gain forgone for others. The resources consumed are not available to provide other treatments. Reimbursement authorities consider these *opportunity costs* of reimbursement as well as the *therapeutic benefit*.

Balancing public health with individual rights

Licensing authorities have a responsibility for protecting and promoting individual rights as well as promoting public health. An individual's right to access a safe and efficacious drug should not be curtailed on the grounds that the drug is not an efficient use of society's resources. The individual has the right to decide whether it is a valuable use of their private resources, and all individuals have that right, equally, including the extremely wealthy who pay for their health care from private resources.

Processes that prioritise some treatments by definition do not treat all individuals equally. When licensing authorities do not treat all individuals equally, it would seem sensible that such unequal treatment should be consistent with the authorities' stated objectives.

Fast tracking and public health.

The FDA and the EMEA operate schemes to reduce the time to licensing for some drugs. These fast track processes gives special treatment to the individuals with the target diseases for the selected therapies. All things being equal, they will receive new treatments more quickly than individuals whose treatments are approved through the standard process. However, the criteria by which therapies are selected for the fast track licensing process are not

obviously focussed on promoting public health; focussed as they are on innovative modes of action and biochemical measures of magnitude of effect.

The advantages of being subject to the fast-track processes can be significant. For example, the EMEA fast-track procedure halves the target time to a decision, compared with the normal licensing process; the FDA fast-track procedure reduces the target time from 10 months to 6 months. Given the revenue streams of block buster drugs, even 4 months additional revenue can represent a substantial benefit.

The FDA accelerated approval process will accept surrogate endpoints. This can have a major impact on the time to licensing as it reduces the duration of trial follow-up. This in turn drives down the cost of phase 3 trials, one of the major costs in pharmaceutical R&D.

As the licensing authorities adopt a disease specific approach to assessing benefit, unless the benefit is confined to mortality, they cannot assess whether fast tracked therapies contribute more or less to the public health than therapies in the standard processes. This problem has long been recognised in the health economics literature with the result that many reimbursement processes accept Quality Adjusted Life Years (QALYs) as a measure of health outcome.[14]

Considering opportunity cost in licensing to promote the public health

Considering the potential harms to the wider community (opportunity costs) necessarily entails an assessment of the likely cost of the therapy. To date, licensing authorities have explicitly and consciously avoided considering the expected cost of the therapies.[18] Rawlins, arguing for more efficient safety testing in pharmaceutical research and development, explicitly discounted a role for price consideration in licensing; arguing that considering price in licensing would ignore citizen's equal right to access safe and effective therapies. Rawlins was also concerned that decision makers would confuse the decision about the safety and efficacy and its cost effectiveness.

We agree with Rawlins that licensing authorities cannot ignore the rights of individuals to access safe and effective treatments that they can afford, just because others cannot afford them. Further, our proposal would not carry the risk of highly effective but expensive treatments would not be licensed. However, it is not inappropriate to consider the expected cost of drugs when choosing whether a particular drug should receive preferential treatment in the licensing process. For these therapies other people's rights to equal treatment within the licensing process has already been abrogated and therefore it is legitimate to consider whether the total benefit to the community is greater than the total harm to the community.

At the beginning of the 21st Century the vast majority of health care is funded through the organisations that have very real resource constraints. The aging population and the causal relationship between age and demand for health care means that these resource constraints are likely to become more not less severe, even if we assume that the cost of health care stabilises. In this environment, licensing authorities' contribution to the public health may be substantially improved by an explicit consideration of the expected cost of the drugs they review.

Some have expressed a concern that a high regulatory hurdle will discourage investment in health care research and development and thus interfere with the innovation cascade that has been observed over the past 50 years. It is undoubtedly true that the utilisation of cost effectiveness in prioritisation would be likely to have some impact upon health care research and development. However, given the success rate of pharmaceutical research and development, where the failure rate at phase 3 is generally accepted to be in the region of 2 out of 3; it does not necessarily follow that more caution in investment would lead to fewer effective therapies arriving at market. This would only be the case if there was no capacity for improving the targeting investment decisions. If this were the case, lower investment would lead to fewer treatments being developed with the same relative success rate and thus a lower number of effective therapies making it to market. However,

there are reasons to believe that the current pricing environments may not promote efficient investment decisions. Typically industry is allowed to amortize the cost of the failed therapies in research and development through the price of the successful treatments. For companies that have a portfolio of treatments in development, a major proportion of the risk of the investment is effectively underwritten by the health care payers' commitment to paying high prices for future successful drugs. If this commitment is tempered, then companies will be more risk averse and we should therefore observe fewer failures in late stage development. It is only if the phase 3 successes systematically tend to have a lower than average probability of success on the basis of phase 2 data, that encouraging more risk averse investments at phase 3 would be expected to lead to fewer successful treatments reaching market.

Section 4: Combining costs, effectiveness and a public health perspective

If we knew which health generating activities would be displaced by the additional resources required by a new technology then we could directly address the question of whether the overall public health would be improved by asking whether the gains in health generated by the new technology exceed the health gains displaced elsewhere in the wider community. In other words the true cost of the technology is the total net health forgone by the community in order to make the therapy available.

Based on some assessment of what is likely to be displaced within the health care system (a cost-effectiveness threshold) [7] we can translate resource costs into health and directly compare health gain to health cost or equivalently convert heath gains into resources and compare the equivalent monetary benefits to monetary costs (see Box 2). These net health or net monetary benefits combine health benefits and costs which fall across the wider community and enable assessment of whether a technology is likely to improve the public health.

When considering provision of the technology for an individual patient, if the net benefit is positive, then there will be a net increase in the public health. Of course the overall contribution of the technology to the public health requires some assessment of the size of the current and future population that could benefit from this technology. The greater the population net benefit, the greater the contribution to the public health. Assuming that the measure of health gain captures all important effects of therapies submitted to the licensing authority, net benefit provides a basis on which the licensing authority can assess the case for fast track review. The licensing authority can then allocate the priority review resources to those therapies which are expected to make the greatest contribution to the public health.

An important characteristic of this system is that the assessment of contribution to the public health would have to be undertaken at the health care system level. This is because it is the interaction between the health care system budget and current activities that determines the cost effectiveness threshold.[7]

As the major licensing authorities serve multiple health care systems, each with different budgets and portfolios of activity, separate net benefit calculations would have to be done for each system, and the results summed. For the purposes of ranking therapies for fast-track licensing, the expected net benefit for health care systems in which the intervention was expected to be negative would be set to zero, on the basis that these systems would not in fact pay for the therapy and therefore the expected health loss would not be incurred. Thus the correct calculation would be to sum the expected net benefit across all health care systems in which expected net benefit was positive.

Section 5: Challenges to implementation of a net benefit approach

The use of net benefit in licensing would face the same criticisms as its use in reimbursement. However, there are some additional potential challenges with using the net benefit approach in licensing. Firstly, if the criterion for fast-tracking is the population net benefit then the probability that a therapy

will be fast-tracked will be directly related to the prevalence of the disease. If society does not wish to see this type of inequality, the individual expected net benefit can be used to select therapies for fast track. This would maintain a link between fast tracking selection and promotion of the public health, although it would no longer maximise the contribution to public health of the fast track system.

Secondly, the difference in the value of a unit of a health gain would vary between systems. Systems with large budgets would attribute greater net benefits for any given therapy. This would mean that therapies for diseases prevalent in wealthier health care systems would be more likely to be fast tracked, which would in turn create an incentive to develop therapies for diseases prevalent in these health care systems. However, the operation of the free market already ensures that there is an incentive to develop therapies for diseases prevalent in countries with the greatest ability to pay. It is not obvious that the use of use of the net benefit framework would make things worse. Indeed, individual nations that wished to promote the development of treatments for disease that were most prevalent in poorer countries could specify an alternative cost effectiveness threshold for evaluating the net benefit of such treatments.

Perhaps more importantly, the variation in the value of a unit of health gain might create incentives for companies to propose lower prices in countries

with lower budgets in order to maximise the expected net benefit across all the health care systems. In such circumstances it would be important that these prices were then implemented in practice.

In principle, there is also an issue of the value of the innovations foregone as a result of reduced incentives to invest in health care research and development. However, as discussed above, this assumes that the current investment behaviours are efficient from a population health perspective. Given the failure rate in phase 2 and 3 of the clinical developments programmes, there is a prima facie case that the level of investment could be reduced without adversely affecting the productivity of the R&D pipeline.

Associated with the argument for considering the option value of the innovation foregone is the observation that incremental advances may act as stepping stones to break through developments. There is a concern that displacing even marginal developments in treatment will disrupt the process of incremental advances and thus threaten subsequent breakthroughs. In principle this is true. However, in the context of promoting public health, the question is whether the net value of the expected future health gain foregone from the incremental benefits and subsequent breakthrough is greater than the expected health benefits from providing incentives for faster access to more cost effective treatments, and potentially for more people.

Benefits of adopting the net benefit framework for priority review

The most obvious benefit of adopting a net benefit framework approach to selecting therapies for priority review is to strengthen the link between the licensing processes and promoting the public health. However, there are other potential benefits; the net benefit framework could promote more efficient production process in manufacturing, and perhaps more importantly, would be particularly valuable in formalising the standards for considering a claim substantiated.

A favourable net benefit can be achieved through either greater efficacy or a lower cost. Thus, a me-too therapy that, through innovation in production technology, came to market at a lower price could qualify for priority review, leading to large gains in public health. This is particularly important for biotech therapies, where the production technologies are developed rapidly, and licensed therapies are often manufactured using older higher cost production technologies. The use of the net benefit framework could introduce a downwards pressure on the price of new therapies. As the net benefit framework quantifies the expected public health benefit from making a therapy available, it facilitates the estimation of the public health benefit foregone if a therapy is not entered into the priority review process.

Regulators have to decide whether the evidence submitted supports the claim of the sponsor that, at the population level, the expected benefits from the use

of the new therapy exceed the expected harms. Historically, little has been written on the evidence required to substantiate a claim. The most recent FDA Modernisation Act notes that whether a claim is considered substantiated "depends upon a number of factors….these include the type of product, the consequence of a false claim, the benefits of a true claim, the costs of developing substantiation for the claim.'.[13]

The net benefit framework allows the quantification and valuation of both the consequences of a false claim and the benefits of a true claim. It has been shown how, in turn these data can be used to establish whether it is efficient to require more evidence prior to approval or give conditional approval whilst more evidence is collected.[5 6] The net benefit framework allows the regulator to place a value on the uncertainty attributable to expedited licensing and the expected health gain foregone from declining to fast-track. It also allows the identification of the important parameters in the decision problem for which additional research is efficient, when conditional approval is provided. Thus the net benefit framework can inform both post-launch (phase IV) research and pharmacovigilance programmes.

By incorporating consideration of uncertainty and total health gain into licensing processes, the net benefit framework may influence decision making with the pharmaceutical research and development process prior to licensing. The use of expedited review as an incentive may promote the development of

therapies that have a higher probability of producing substantial health gain and by implication reduce or remove the incentive to develop therapies of marginal value compared to therapies already on the market. This in turn could lead to a higher threshold for positive decisions on the transition to phase 3 trials. All things being equal this could lead to fewer failures in Phase 3. As the need to amortise the cost of failures in phase 3 is one of the major contributory factors to the high cost of developing new therapies, there is the potential for a reduction in the average cost of developing new therapies.[9]

The degree to which any of these effects would be observed depends upon the magnitude of the advantage available from the fast track system. If licensing authorities accepted the appropriateness of using fast track review systems to promote public health, they could vary the characteristics of the fast track system as a signalling mechanism.

Summary

Historically, pharmaceutical licensing authorities have acted as consumer protection organisations, ensuring that drugs are safe and manufacturers' claims are reasonable. This model of licensing was consistent with health care consumption being primarily a decision made by individual citizens and funded from the private resources. Increasingly health care consumption is determined by system wide guidelines rather than individual preferences and it is financed from either general taxation or social insurance. Against this

background, it may be appropriate for licensing authorities to adopt a broader remit than consumer protection.

In this paper we have argued that when the price of a therapy has a substantial impact upon the proportion of the population that can access them, it is appropriate, legitimate and feasible for licensing authorities such as the FDA and the EMEA to use the expected net benefit of a new therapy as the basis on which to identify therapies for expedited review.

The proliferation of fourth hurdle organisations across the developed world, including the USA, has implications for the suitability of the current pharmaceutical licensing frameworks. Now may be the time for the licensing authorities to engage with a value based regulation paradigm.

References

1. ABPI House of Commons Health Select Committee Inquiry in the National Institute for Clinical Excellence: Submission from the Association of the British Pharmaceutical Industry 10 January 2002 http://www.abpi.org.uk/information/industry_positions/NICE%20-%20select%20committee%20submission%20ABPI%20final.doc (accessed 18th November 2005)
2. Angell, M. Excess in the Pharmaceutical Industry CMAJ 2004;171:12
3. Brazier J.E. Deverill M. Green C. Harper R. Booth A. A review of the use of health status measures in economic evaluation Health Technology Assessment 1999;3(9)
4. Canadian Agency for Drugs and Technologies in Health Guideline for the economic evaluation of health technologies: Canada 3rd Edition 2006
   http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf (accessed 12th April 2006)
5. Claxton K, Neuman PJ, Araki SS, Weinstein MC. The value of information: an application to a policy model of Alzheimer's disease. International Journal of Technology Assessment in Health Care 2001;17:38-55.
6. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence. Lancet 2002;360:711-715.
7. Culyer AJ., McCabe C., Briggs, AH., Claxton K., Buxton, M. Akehurst R., Sculpher M., and Brazier JE. Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence. J. Health Serv. Res. Policy 2007 12;1:56-58
8. Detels, R. et al. (Eds) Oxford Textbook of Public Health Oxford OUP 2002

9. DiMasi, J.A., Hansen, R.W., and Grabowski, H.G. The price of innovation: new estimates of drug development costs. Journal of Health Economics 2003;22(2):151-185
10. Drummond, M.F., Sculpher M.J., Torrance G.W., O'Brien, B.J., Stoddart, G.L., Methods for the Economic evaluation of Health Care Programmes. Third Edition OUP 2005 Oxford
11. European Medicines Evaluation Agency http://www.emea.eu.int/mission.htm (accessed 1st September 2005)
12. Food and Drug Administration http://www.fda.gov/opacom/morechoices/mission.html (accessed 1st September 2005)
13. CMS CMS Legislative Summary April 2004: Summary of HR1: Medicare prescription drug improvement and modernization act of 2003. Public Law 10-173 http://www.cms.hhs.gov/MMAUpdate/downloads/PL108-173summary.pdf (accessed 10th December 2007)
14. ISPOR PharmacoEconomic Guidelines around the world. International Society for PharmacoEconomics and Outcomes Research (ISPOR) http://www.ispor.org/PEguidelines/index.asp (accessed 24th November 2005)
15. National Institute for Clinical Excellence Guide to the Methods of Health Technology Appraisal NICE London April 2004
16. Palmer S. Smith PC. Incorporating option values into the economic evaluation of health care technologies. Journal of Health Economics 2000;19(5):755-766
17. Pharmaceutical Benefits Advisory Committee. Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee (PBAC): including major submissions involving economic evaluations. http://www.health.gov.au/internet/wcms/publishing.nsf/Content/

health-pbs-general-pubs-guidelines-index.htm (accessed 12th April 2006)

18. Rawlins, M. Cutting the cost of drug development? Nature: Drug Discovery 2004;3:360-362
19. United States Congress. Public Law 104-170 - US Food Quality Protection Act 1996
20. Yogendra, S. The US Food Quality Protection Act: A review of the dynamics of pesticide regulation and firm responses. Innogen Working Paper 11 July 2004.

Box 1: Fourth Hurdle Organisations

Pharmaceutical Benefits Advisory Committee	Australia
Canadian Agency for Drugs and Technologies in Health	Canada
Haute Autorite Sante	France
Institute for Quality and Efficiency in Health Care	Germany
Pharmacy Advisory Committee	New Zealand
Norwegian Medicines Evaluation Centre	Norway
National Institute for Health and Clinical Excellence	United Kingdom

Box 4: Net Benefit

Incremental Cost Effectiveness Ratio (ICER) = $\Delta C / \Delta E$

Net Monetary Benefit (NMB) = $R_T \Delta E - \Delta C$

Net Health Benefit (NHB) = $\Delta E - (\Delta C / R_T)$

R_T = Threshold Ratio; ΔC = Difference in mean cost between comparators;

ΔE = Difference in mean effect between comparators